Synthesis of 1,2,3-triazoles and biological evaluation

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Summary

Over the past decade, organocatalytic synthetic procedures have emerged as an essential part of triazole chemistry. In order to avoid various obstacles of metal catalyzed synthesis of triazoles in biological systems, various organocatalyzed syntheses were developed.

This thesis is dedicated to the exploration of various triazolization strategies towards functionalized 1,2,3-triazole moieties and studies of their activities against cancer cell as well as viral cell lines. These triazolization strategies rely on inexpensive and readily available starting materials.

In chapter 1 a brief summary of previously discovered organocatalyzed methodologies towards functionalized 1,2,3-triazoles as well as their biological study and the synthesis of biologically active molecules containing triazole as a core unit has been presented concisely. The goals and objectives of this thesis are also elaborated in this chapter.

Chapter 2 describes a three-component reaction of readily available starting materials such as enolizable ketones, primary amines, and para-nitrophenyl azide leading to trisubstituted triazoles. This newly developed methodology has been used to functionalize various natural compounds and to synthesize various multifunctional building blocks.

Chapter 3 is dedicated to the formation of *NH*-1,2,3-triazoles from readily available starting materials such as enolizable ketones, ammonium acetate, and para-nitro phenyl azide. The utility of the reaction has further demonstrated by direct conversion of compounds containing enolizable keto groups to the corresponding triazole heterocycles.

Chapter 4 elucidates a highly efficient and regiospecific $Zn(OAc)_2$-mediated synthesis of propargyl functionalized triazole derivatives in a single step from ketones and propargyl amine. This methodology has given access to a special type of triazoles which are not possible to synthesize by other means. Furthermore, we have discussed the functionalization of propargyl triazoles with azides *via* click reaction to form an unique type of N-C linked bis-triazoles.

Chapter 5 represents an unprecedented Rh(II)-catalyzed selective decomposition of bis(1,2,3-triazoles) followed by [3 + 2]-intramolecular annulation reaction which leads to the formation of 3,4-fused indoles. Extension of this protocol to heterocycles leads to interesting polyfused 1,2,3-triazole derivatives.
In chapter 6 a series of newly functionalized artemisinin derivatives has been prepared using an organocatalytic multicomponent reaction in order to study their activity in viral cell lines.
Chapter 7 deals with the development of three synthetic strategies to access 1,4-disubstituted, 1,5-disubstituted, and fused 1,2,3-triazoles analogues of artemisinin with promising anticancer activity.

Samenvatting

Het afgelopen decennium is de organokatalytische synthese op de voorgrond getreden als een essentieel deel van de triazoolchemie. Om de obstakels te overkomen die metaal-gekatalyseerde syntheses van triazolen met zich meebrengen in biologische systemen, werden verscheidene organokatalytische methodes ontwikkeld.

Dit thesisproject behandelt de ontwikkeling van verschillende strategieën voor de synthese van gefunctionaliseerde 1,2,3-triazolen en hun biologische activiteit tegen kanker- en virale cellijnen. De ontwikkelde triazoleringsmethodes zijn gebaseerd op het gebruik van goedkope, commerciële startmaterialen.

In hoofdstuk 1 zal een beknopte samenvatting gegeven worden van de reeds ontdekte organokatalytische methodes ter vorming van gefunctionaliseerde 1,2,3-triazolen evenals de uitgevoerde biologische studies en syntheses van biologisch actieve molecules die een triazool bevatten als kern van de structuur. Daarnaast zullen de doelstellingen van deze thesis ook worden uitgewerkt in dit hoofdstuk.

Hoofdstuk 2 beschrijft een drie-componentsreactie van beschikbare startmaterialen zoals enoliseerbare ketonen, primaire amines en 4-nitrofenylazide die leiden tot trigesubstitueerde triazolen. Deze nieuw ontwikkelde methode werd gebruikt in de functionalisatie van verscheidene natuurproducten en voor de synthese van verschillende multifunctionele bouwstenen.

Hoofdstuk 3 is toegewijd aan de synthese van *NH*-1,2,3-triazolen van commercieel beschikbare startmaterialen, zijnde enoliseerbare ketonen, ammoniumacetaat en 4-nitrofenylazide. Het nut van deze reactie werd verder geïllustreerd door de directe conversie van producten met een enoliseerbare ketongroep naar de overeenkomstige triazoolstructuren.

Hoofdstuk 4 licht een zeer efficiënte en regiospecifieke $Zn(OAc)_2$-gemedieerde synthese toe van propargyl gefunctionaliseerde triazoolderivaten in één stap vanuit ketonen en propargylamine. Deze methode geeft toegang tot een speciaal type van triazolen die niet

synthetiseerbaar zijn *via* de gerapporteerde methodologieën. Bovendien wordt de functionalisatie van propargyltriazolen met azides *via* de clickchemie besproken, waardoor een uniek type van N-C verbonden bistriazolen kan gemaakt worden.

Hoofdstuk 5 stelt een ongekende selectieve ontbinding voor van bistriazolen door een Rh(II)-gekatalyseerde [3+2]-intramoleculaire annuleringsreactie die leidt tot de vorming van 3,4-gefuseerde indolen. Het uitbreiden van dit protocol naar heterocyclische structuren leidt tot interessante polygefuseerde 1,2,3-triazoolderivaten.

In hoofdstuk 6 werd een serie van nieuwe, gefunctionaliseerde artemisininederivaten geproduceerd door gebruik te maken van een organokatalytische multicomponentsreactie, waarna hun biologische activiteit in virale cellijnen bestudeerd kon worden.

In hoofdstuk 7 wordt de ontwikkeling van drie synthetische procedures behandeld, waarbij 1,4-digesubstitueerde, 1,5-digesubstitueerde en gefuseerde 1,2,3-triazoolanaloga van artemisinine, met veelbelovende antikankeractiviteit, toegankelijk gemaakt worden.

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Chapter 1

General Introduction and Objectives

1. General introduction

1.1 Overview of 1,2,3-triazoles

Nitrogen-containing heterocycles are one of the important compounds found in organic chemistry as well as in the pharmaceutical industry. Among these, 1,2,3-triazoles have drawn considerable attention in the chemical community. The application of triazoles has emerged in each corner of pharmaceutical research including derivatives with anticancer, antibacterial, antiviral, and antifungal properties.[1] In addition to the pharmaceutical applications, they have also been proposed for industrial applications such as lubricants, photo-stabilizers, and dyes.[1]

Depending on the position of the substituent on the nitrogen atom, there are mainly two types of 1,2,3-triazoles which are 1H or 3H-1,2,3-triazole, and 2H-1,2,3-triazole (Figure 1).

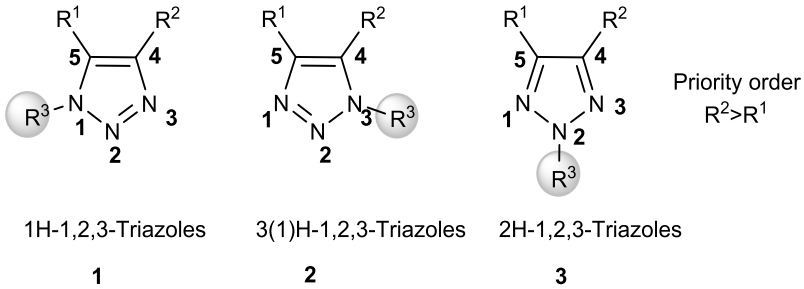


Figure 1 different types of 1,2,3-triazole

NH-triazoles exist in three thermodynamically interchangeable tautomeric forms **4**-**6**. However, ^{14}N and ^{15}N NMR data unveil that tautomer **5** is present in 70-100% proportion (Figure 2).[2]

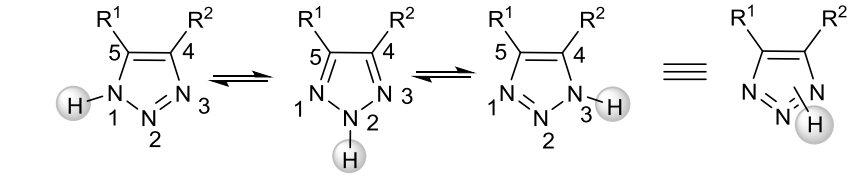
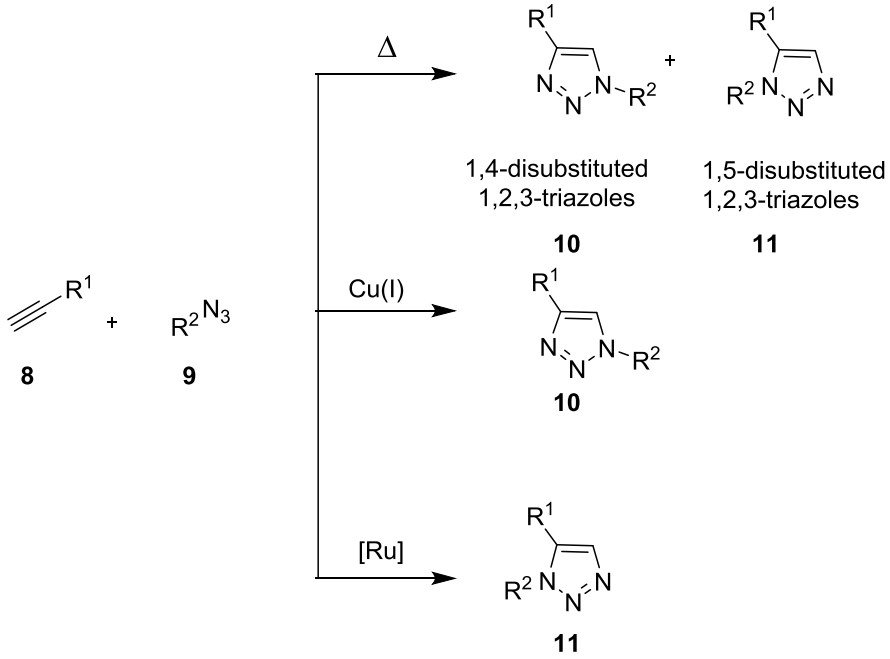


Figure 2 various tautomeric forms of NH-1,2,3-triazoles

1.2 Various synthetic approaches towards the synthesis of functionalized 1,2,3-triazoles

1,2,3-Triazoles are known as amide surrogates due to the high dipole moment and high H-bonding capabilities, and in fact have a higher metabolic stability than the amide bond.[3] 1,2,3-Triazoles were first synthesized by 1,3-dipolar cycloaddition reaction of azides and alkynes at high temperature without any selectivity, which is called the Huisgen cycloaddition reaction (Scheme 1).[4] This reaction has not been applied widely in organic synthesis due to the high temperature, poor regioselectivity, and low chemical yield.

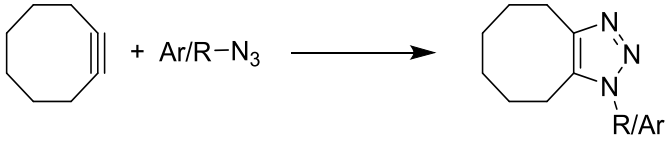
Later, in 2001, Sharpless and Meldal independently introduced a regioselective synthesis of 1,4-disubstituted 1,2,3-triazoles *via* copper(I)-catalyzed azide-alkyne cycloaddition, which is widely known as the "click reaction" (Scheme 1).[5] The Cu(I)-catalyzed azide-alkyne cycloaddition reaction has been broadly accepted in the chemical community due to the following reasons: a) copper accelerates the cycloaddition process about 10^8 times, b) the reaction can proceed in a broad range of temperatures, c) it is insensitive to water, d) the reaction has broad functional group tolerance, e) the compounds may often be purified by extraction or filtration without any column chromatography, and f) the reaction is insensitive to a pH range from 4 to 12.



Scheme 1 synthesis of 1,2,3-triazoles via Huisgen and metal catalyzed cycloaddition reaction

Soon after the discovery of the click reaction, another complementary discovery was achieved by the ruthenium catalyzed cycloaddition of alkynes and azides to exclusively form 1,5-disubstituted 1,2,3-triazoles (Scheme 1)[6]. However, high reaction temperature, low yield, and the use of expensive metal catalysts restricts this reaction to become widely applicable.

The metal catalyzed synthesis of 1,2,3-triazoles is limited by the fact that toxicity of the metal catalyst hampers wider exploration in biological systems[7]. Hence an alternative strategy was required to avoid metal catalysts. As one possible approach, the strain promoted azide alkyne cycloaddition (SPAAC) reaction was developed by Bertozzi and co-workers (Scheme 2)[8]. This reaction involves the cycloaddition between azides and cyclooctynes, which results in the formation of 1,2,3-triazoles without any toxic metal catalyst. This reaction gives access to the *in vitro* modification of various biomolecules.

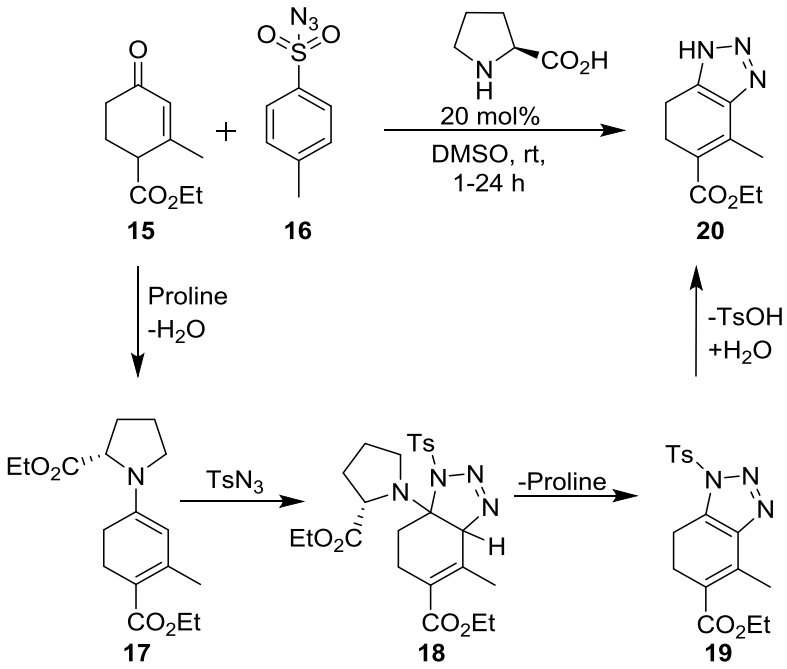


Scheme 2 strain promoted azide alkyne cycloaddition (SPAAC) reaction

In recent years, organocatalytic click reactions have received much attention in the chemical community due to the broad application of 1,2,3-triazoles in various fields of chemistry. The organocatalytic reactions can be organized into five categories: a) enamine-mediated synthesis, b) iminium mediated synthesis, c) enolate-mediated synthesis, d) alkynes precursors, and e) activated alkenes as dipolarophiles.

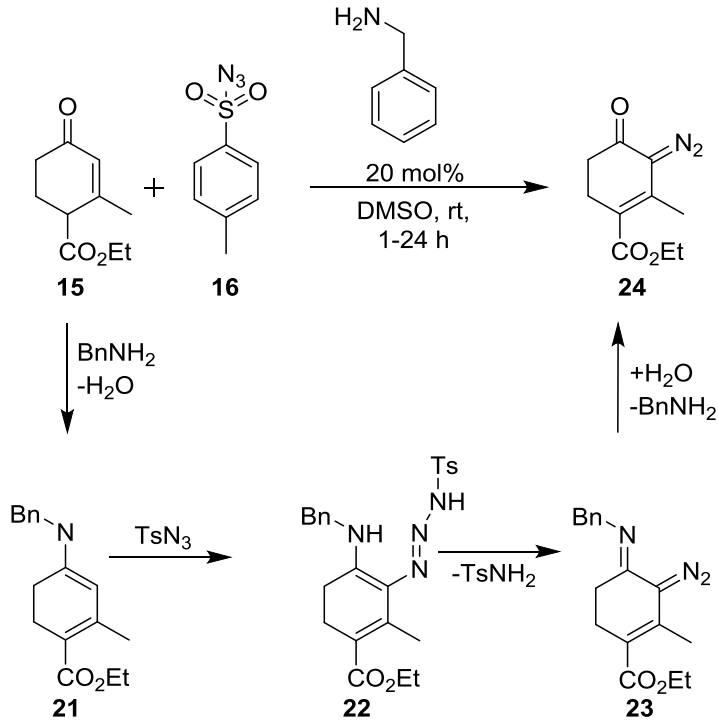
1.2.1 Enamine-mediated synthesis

In 2008 the Ramachary group was the first to report an L-proline catalyzed synthesis of 1,2,3-triazoles from Hagemann's ester (Scheme 3).[9] According to the authors, the reaction proceeds through an enamine intermediate **17**, which is formed when Hagemann's ester was treated with the proline catalyst. The resulting enamine **17** undergoes a [3+2] cycloaddition with tosyl azide leading to the formation of the triazoline intermediate **18**, which transforms into the fused tosyl triazole **19** *via* elimination of proline catalyst. *NH*-1,2,3-triazole **20** was formed *via* an *in situ* hydrolysis by water present in the DMSO solvent.



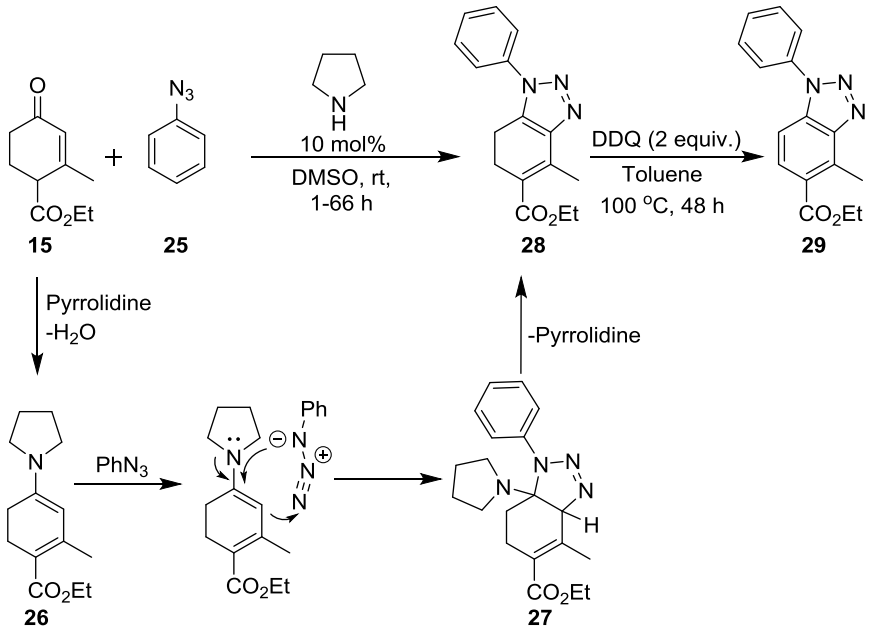
Scheme 3 synthesis of *NH*-1,2,3-triazoles from Hagemann's esters

Interestingly, when L-proline was changed to benzylamine, the final product formed was an α-diazo ketone. The detailed mechanism of this reaction as proposed by the authors[9] is shown in scheme 4 below. An alternative explanation is the Regitz diazo transfer to an enolate generated from the ester with the benzylamine base.



Scheme 4 synthesis of α-diazo ketone

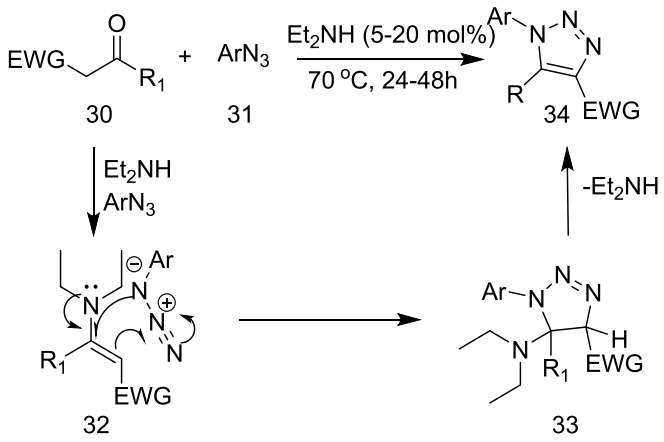
N-Aryl-benzotriazoles can be synthesized by a Buchwald-Hartwig-type of arylation of *NH*-benzotriazoles. The Ramachary group again reported an alternative synthesis based on their previous synthetic method to access *N*-aryl cyclohexadienotriazoles starting from the Hagemann's esters and an azide in the presence of pyrrolidine as a catalyst (Scheme 5).[10] The formed triazoles **28** are subsequently oxidized to the benzotriazoles **29** by using DDQ.



Scheme 5 Synthesis of *N*-aryl-benzotriazoles from Hagemann's esters

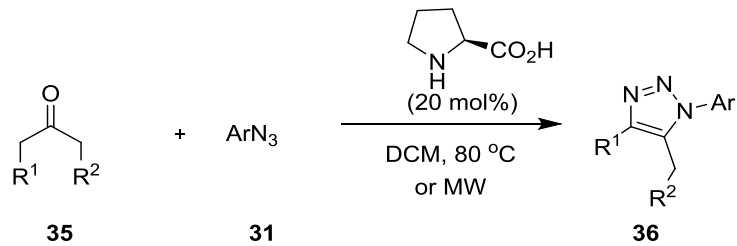
The above methodologies described by the Ramachary group have a serious drawback which is the narrow scope of the Hagemann's esters with α,β-unsaturated keto group.

In 2011, Wang *et al.* described an organocatalytic cycloaddition reaction of different azides and enamines derived from β-carbonyl compounds and secondary amines affording the 1,4,5-trisubstituted 1,2,3-triazoles (Scheme 6).[11] This reaction has several advantages such as a) broad functional group tolerance b) regioselective product formation, c) high yield, d) diversity in the products. According to the authors, the reaction proceeds through a 1,3-dipolar cycloaddition reaction between the electron rich enamine **32** and an aryl azide **31**, leading to the regioselective formation of triazoline intermediate **33**. The triazole **34** product is formed *via* elimination of the amine catalyst from the triazoline intermediate **33**.



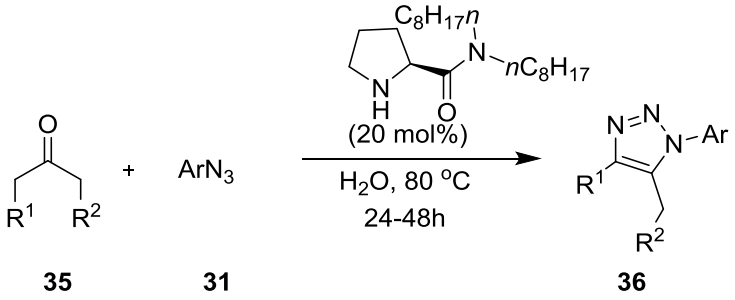
Scheme 6 synthesis of 1,4,5-trisubstituted 1,2,3-triazoles from β-carbonyl compounds

All the previously discussed methods are restricted to activated carbonyl compounds. To overcome this obstacle, the groups of Wang and Pons-Bressy independently reported an organocatalytic reaction between unactivated ketones and aromatic azides to afford 1,2,3-triazoles.[12] According to Pons-Bressy, ketones and azides were heated at 80 °C for 100h in the presence of 20 mol% catalyst to afford the desired triazolized product in excellent yield (Scheme 7). Interestingly, the reaction time can be decreased to 1h by microwave-heating without compromising the yield. This reaction also occurs via a similar enamine intermediate as discussed earlier (Scheme 6). The major disadvantage of this reaction is that aliphatic azides were not reactive enough under the reported conditions.



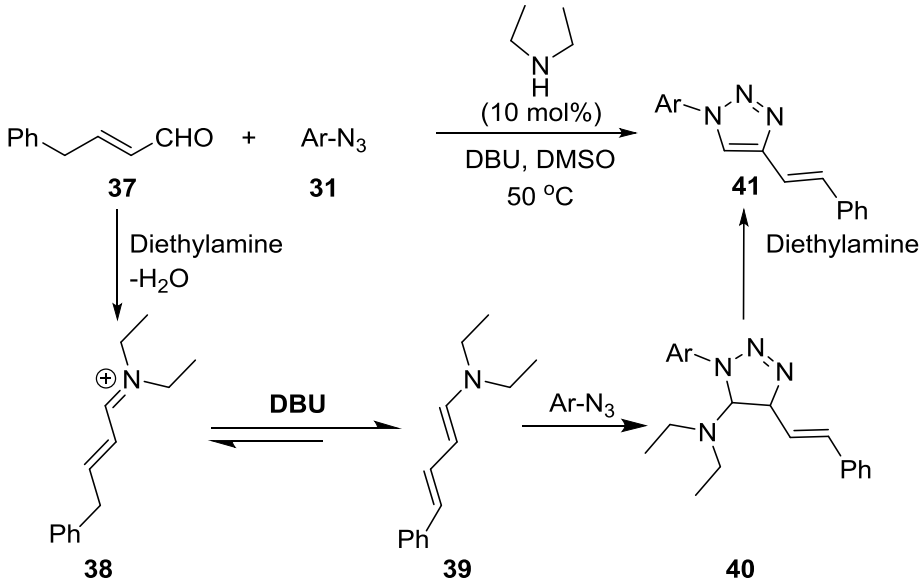
Scheme 7 synthesis of 1,4,5-trisubstituted 1,2,3-triazoles from enolizable ketones

Organic solvents were employed for all the reaction methods described earlier, which could restrict their application in biological systems. In order to develop a biocompatible procedure, Wang discovered a proline based amphiphilic amine catalyzed synthesis of 1,2,3-triazoles in water medium (Scheme 8).[13] Due to the presence of the long lipophilic chain in the catalyst, the reaction occurs in the hydrophobic part of the catalyst. According to the authors, a tertiary amide was required rather than a secondary amide which indicates that the reaction takes place in catalytic micelles.



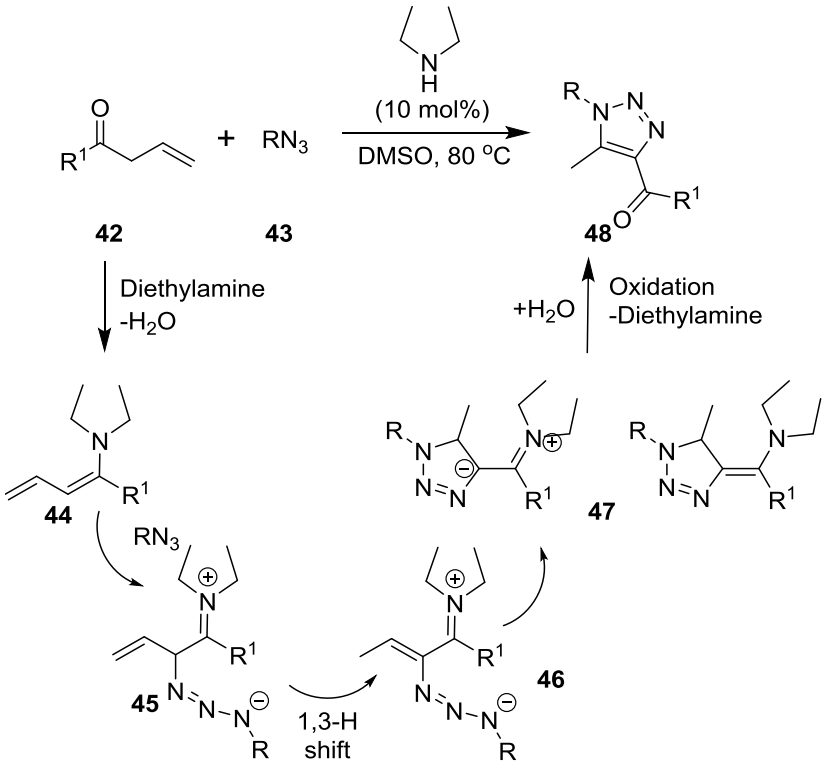
Scheme 8 synthesis of 1,4,5-trisubstituted 1,2,3-triazoles from enolizable ketones

Soon after that, a straightforward organocatalytic route towards the synthesis of 4-alkenyl-1,2,3-triazoles has been reported by the same group.[14] The unsaturated aldehydes were heated at 50 °C with aromatic azides in presence of 10 mol% diethylamine and 10 mol % of DBU for 2h in presence of DMSO as a solvent. It has been found that both diethylamine and DBU were required for optimal yields. The reaction was found to be very general regardless of any electron withdrawing and electron donating groups on the unsaturated aldehydes or aryl azides. However, aliphatic azides gave a very low yield. The reaction proceeds through an enamine intermediate **38** which undergoes DBU induced deprotonation to form dienamine **39**. Then the cycloaddition takes place between dienamine **39** and aryl azide **31** to afford triazoline intermediate **40**. Finally, the triazolized product **41** is formed *via* elimination of diethylamine from triazoline intermediate **40** (Scheme 9).



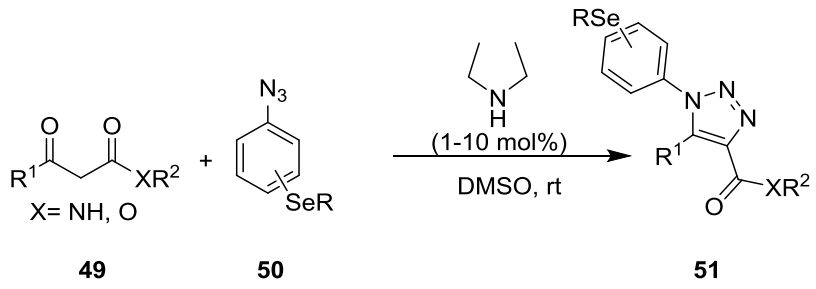
Scheme 9 synthesis of 4-alkenyl-1,2,3-triazoles from α, β -unsaturated ketone

Wang and co-workers developed the synthesis of 4-acyl triazoles starting form allyl ketones and aryl azides in the presence of a catalytic amount of diethylamine (Scheme 10)[15]. The reaction could be successfully implemented on allyl and aryl ketones bearing either electron donating or electron withdrawing groups. The electronic effect of substituents on the aryl ring of the azide did also not affect the outcome of the reaction. According to the authors, the reaction proceeds through an enamine intermediate **44**, which reacts with aryl azide to furnish the intermediate **45**. The intermediate **45** undergoes a 1,3-H shift to form the intermediate **46**. After that, an intramolecular cyclocondensation leads to the triazolized product **47**. The final product **48** is formed after hydrolysis and oxidation of **47**.



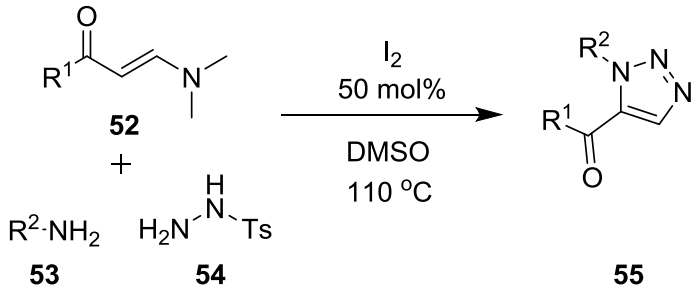
Scheme 10 synthesis of acyl triazoles

Soon after that, the group of Alves-Paixão has reported an organocatalytic synthesis of the arylselenyl-1,2,3-triazoles starting from active methylene compounds and arylselenides **50** in presence of catalytic amount of diethylamine (Scheme 11).[16] Both β-keto ester and amides have been used successfully in this reaction.



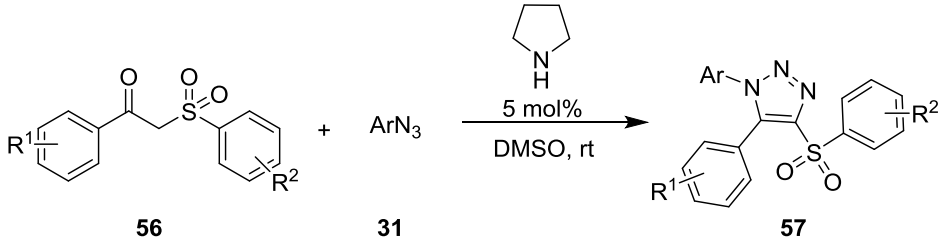
Scheme 11 synthesis of the arylselenyl-1,2,3-triazoles from active methylene compounds

Wan and co-workers in 2015 have reported an organocatalytic method towards the synthesis of 1,5-disubstituted 1,2,3-triazoles starting from enamines, primary amines and tosylhydrazine **54** in the presence of iodine (Scheme 12).[17]



Scheme 12 synthesis of 1,5-disubstituted 1,2,3-acyl triazoles

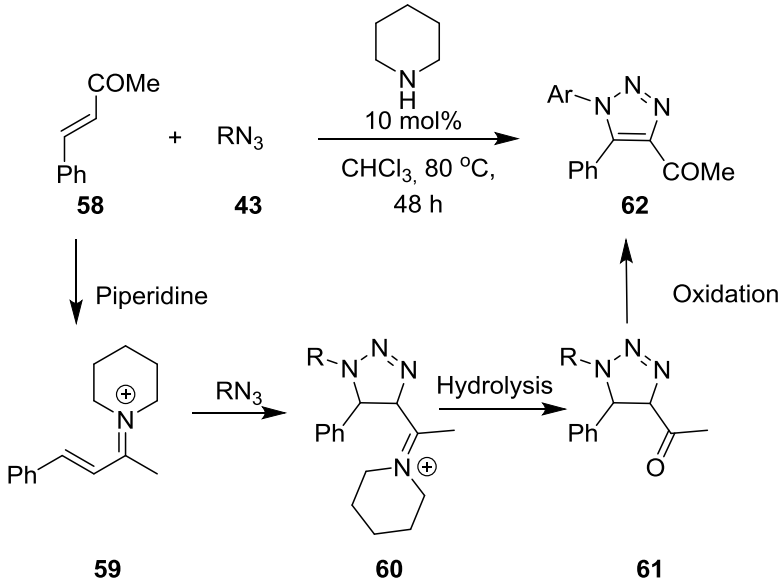
Soon after that, Alves and co-workers developed a pyrrolidine catalytic enamine-azide [3+2] cycloaddition reaction of aryl azides **31** and β-keto sulfones **56** to afford the corresponding sulfonyl triazoles **57**. The reaction was performed at room temperature in DMSO with 5 mol% of pyrrolidine (Scheme 13). This reaction is found to be applicable to a variety of aryl azides and β-keto aryl sulfones.



Scheme 13 synthesis of 1,4,5-trisubstituted 1,2,3-sulfonyl triazoles

1.2.2 Iminium mediated synthesis

Recently Wang *et al.* reported an organocatalytic method towards the synthesis of trisubstituted 1,2,3-triazoles (Scheme 14).[18] The reaction was shown to be applicable to a wide range of azides such as aromatic, aliphatic and heteroaromatic species. The reaction was reported to proceed through an iminium intermediate **59**. The triazoline intermediate **60** was formed after cycloaddition of the iminium intermediate **59** with the azides. The final product **62** is formed after hydrolysis and air oxidation of triazoline intermediate **61**.

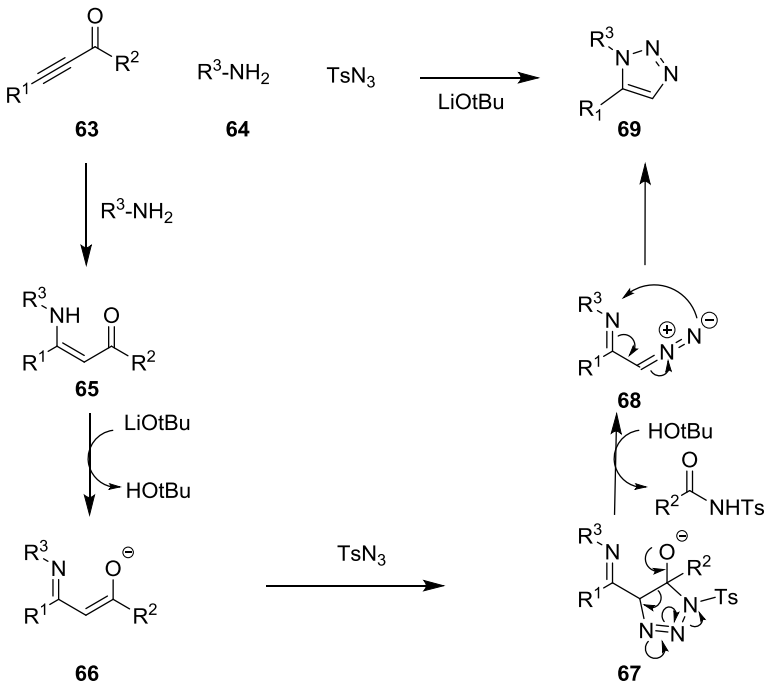


Scheme 14 synthesis of ester substituted 1,2,3-triazoles

1.2.3 Enolate mediated synthesis

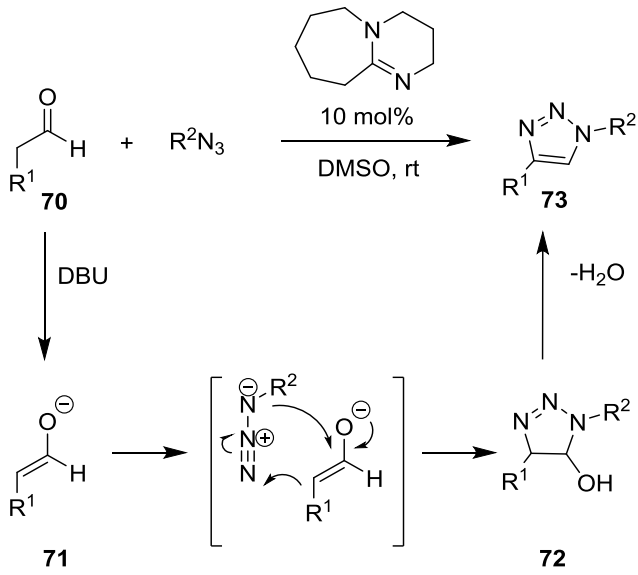
The enolate mediated organocatalytic synthesis of 1,2,3-triazoles was first demonstrated by Cui *et al.* in 2013 starting from propynones, primary amines, and tosyl azides using lithium *tert*-butoxide as a base (Scheme 15).[19] According to the authors, the mechanism is initiated by the Michael addition of amines to propynones to form α,β-unsaturated ketone **65**. After that, the enolate intermediate **66** is formed in the presence of Li*O*t*Bu. Then, the cycloaddition of tosyl

azide with **66** leads to triazoline intermediate **67** which transformed to diazo species **68** by eliminating an amide molecule. The diazo species **68** leads to final product **69** by spontaneous 1,5-dipolar cyclisation.[19]



Scheme 15 synthesis of 1,5-disubstituted triazoles from α, β -unsaturated ketone

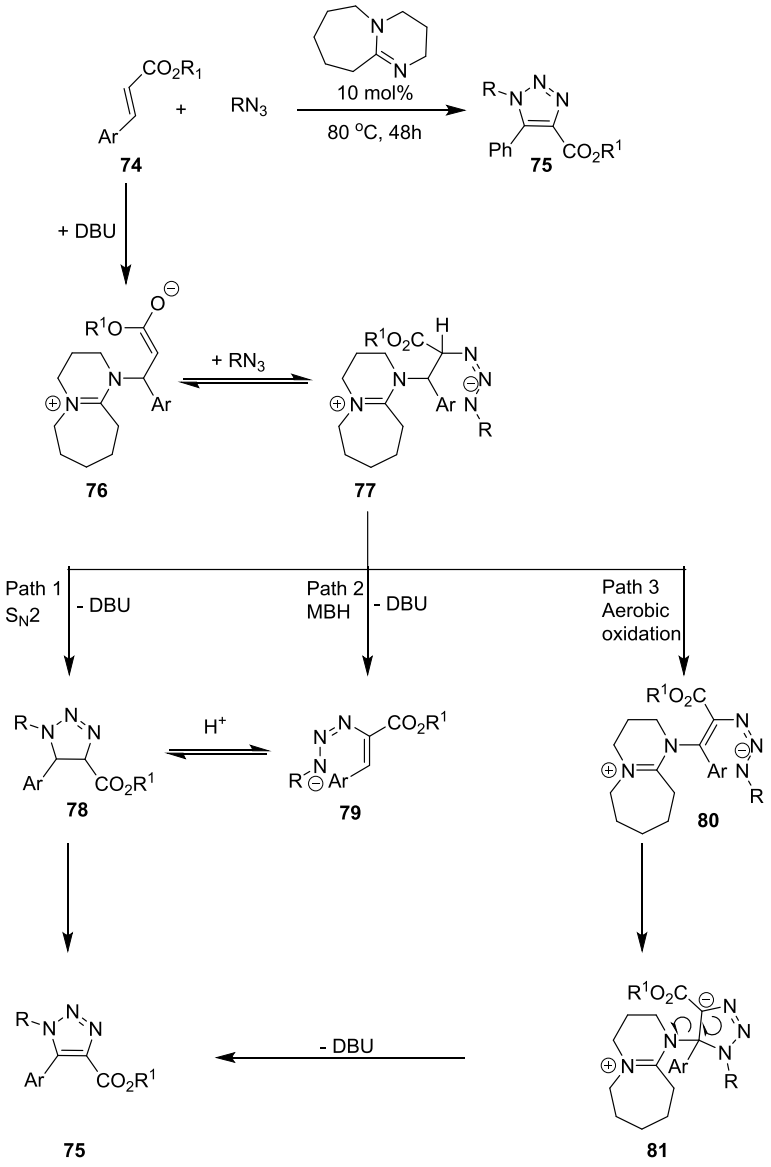
Soon after that, Ramachary *et al.* have reported an organocatalytic enolate mediated synthesis of 1,4-disubstituted 1,2,3-triazoles from enolizable aldehydes and aryl azides in the presence of 10 mol% DBU (Scheme 16). Both electron poor and electron rich aldehydes are found to give good yields in the standard reaction conditions. According to the authors, the enolate **71** is formed in the presence of DBU. This intermediate enolate **71** subsequently undergoes a [3+2] cycloaddition with the respective azide to form the triazoline intermediate **72**. The final product **73** is formed after elimination of a water molecule (Scheme 16).[20]



Scheme 16 synthesis of 1,4-disubstituted 1,2,3-triazoles from enolizable aldehyde

The first organocatalytic aerobic oxidative intermolecular azide zwitterionic cycloaddition was reported by Wang *et al*. (Scheme 17). [21] A diverse set of activated alkenes such as α,β-unsaturated amides, esters, ketones, aldehydes, and nitriles were applied successfully under the reported reaction conditions. In addition, aliphatic and aromatic azides were also well tolerated under the reaction circumstances. According to the author, the reaction proceeded through a zwitterionic enolate intermediate **76**, formed by the reaction between the α,β-unsaturated ester and DBU. Next, the addition of the zwitterionic enolate **76** onto the azide takes place which leads to the formation of intermediate **77**. The intermediate **77** generates the final product by three possible pathways. The first possible pathway is the generation of 4,5-dihydrotriazole **78** via an intramolecular S_N2 reaction of **77**. The second pathway involves the E_2 elimination of DBU, resulting in the formation of the intermediate **79**. A 6π electrocyclization followed by an aerobic oxidation leads to the final product **75**. In the final pathway, at first olefin intermediate **80** is formed by aerobic oxidation of **77**. Then the intermediate **80**

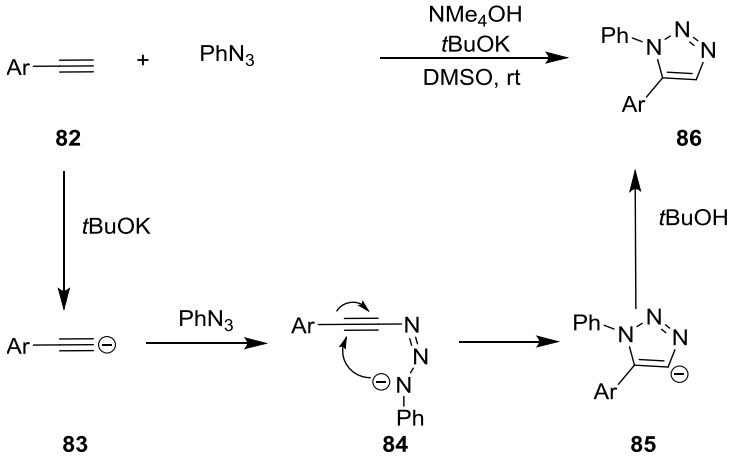
undergoes 6π cycloaddition leading to intermediate **81**, which liberates DBU to furnish the final product **75** (Scheme 17).



Scheme 17 synthesis of ester substituted 1,2,3-triazoles

1.2.4 Alkynes and alkyne precursors

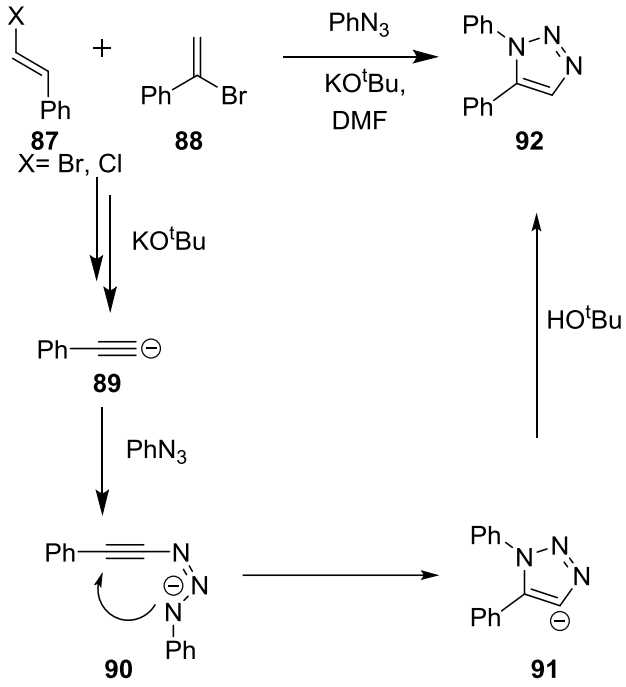
Although enolizable ketones and aldehydes are most commonly used as a starting precursor for organocatalytic synthesis, a limited number of reports are there where alkynes are used as a starting material for metal free triazole synthesis. For instance, Fokin *et al.* were the first to report a metal free organocatalytic synthesis of 1,5-disubstituted 1,2,3-triazoles starting from alkynes and azides (Scheme 18).[22] The reaction was carried out in the presence of 10 mol% of NMe_4OH and ^{t}BuOK as catalyst. According to the authors, electron deficient aryl azides and sterically crowded azides afforded lower yields. Similarly, electron deficient alkynes also afforded lower yield. The mechanism is proposed to start with the formation of aryl acetylide **83**. The triazenide intermediate **84** is formed after nucleophilic attack of aryl acetylide to azide, and undergoes a 5-*endo*-*dig* cyclization which results in the formation of the 1,5-disubstituted 1,2,3-triazolyl anion **85**. In the end, the final product **86** is obtained via protonation by *t*BuOH (Scheme 18).



Scheme 18 Synthesis of 1,5-disubstituted 1,2,3-triazoles from alkynes

Similarly, Lin *et al.* reported 1,5-disubstituted triazoles starting from vinyl halides *via in situ* generation of alkynes in the presence of base

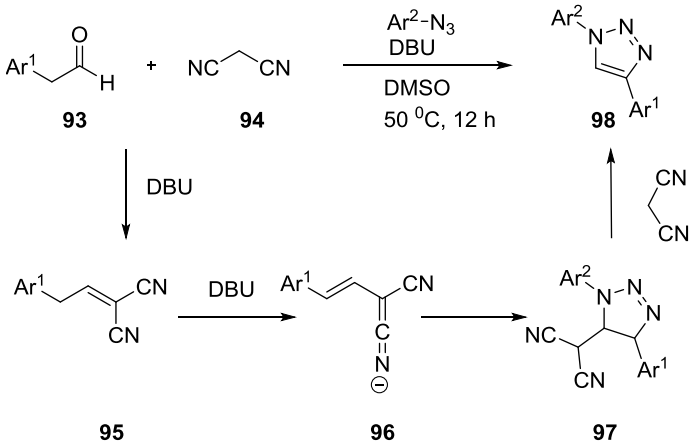
(Scheme 19).[23] Here the mechanism proposed by Lin *et al.* is similar to the one previously reported by Fokin *et al.* [22]



Scheme 19 synthesis of 1,5-disubstituted 1,2,3-triazoles from vinyl halides

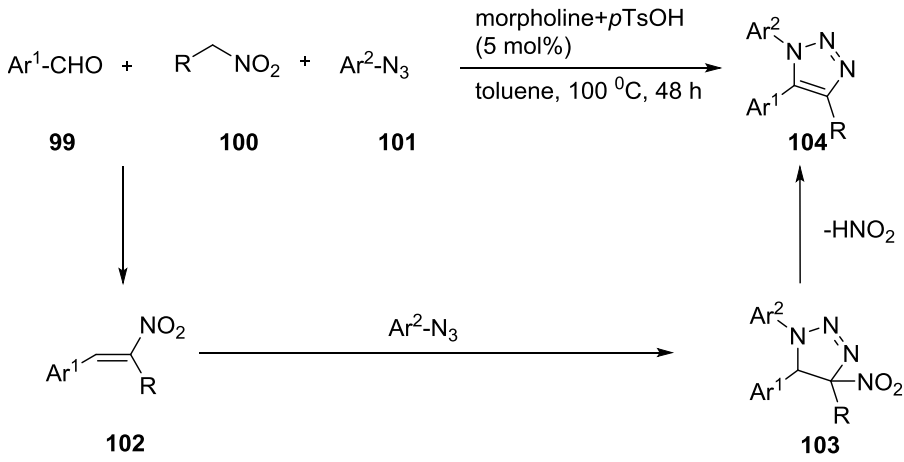
1.2.5 Activated alkenes as dipolarophiles

Paixão *et al*. reported an efficient method to access 1,4-disubstituted 1,2,3-triazoles with high regioselectivity (Scheme 20).[24] The reaction was carried out in the presence of a catalytic amount of DBU. The reaction proceeds through the Knoevenagel condensed product **95** which is formed from an enolizable aldehyde **93** and malononitrile **94**. Subsequently, deprotonation by DBU resulted in the formation of a vinylogous carbanion **96**, which undergoes cycloaddition with the azide to form the intermediate **97**. Finally, elimination of malononitrile leads to the final product **98**. Despite of having advantages such as low temperature and high yield, this reaction is not applicable for aliphatic azides.



Scheme 20 synthesis of 1,4-disubstituted 1,2,3-triazoles from enolizable ketones

Despite the advancements in organocatalytic triazole synthesis, there have been no reports on the multicomponent reaction towards the synthesis of triazoles. For the first time, Dehaen *et al.* reported an organocatalytic reaction towards the synthesis of 1,4,5-trisubstituted 1,2,3-triazoles starting from aldehydes, nitroalkanes and azides in one pot (Scheme 21).[25] The reaction is carried out in the presence of *p*-toluenesulfonic acid morpholine salt as a catalyst. Thus, the Knoevenagel condensed product **102** was formed from aldehyde **99** and nitroalkane **100**. The condensed product **102** acts as a dipolarophile which undergoes regioselective Huisgen cycloaddition with azide **101** to form triazoline intermediate **103**. The final product **104** was formed by elimination of nitrous acid. The reaction tolerates aromatic, heteroaromatic, and aliphatic aldehydes. In addition, the reaction is applicable to aromatic as well as aliphatic azides.

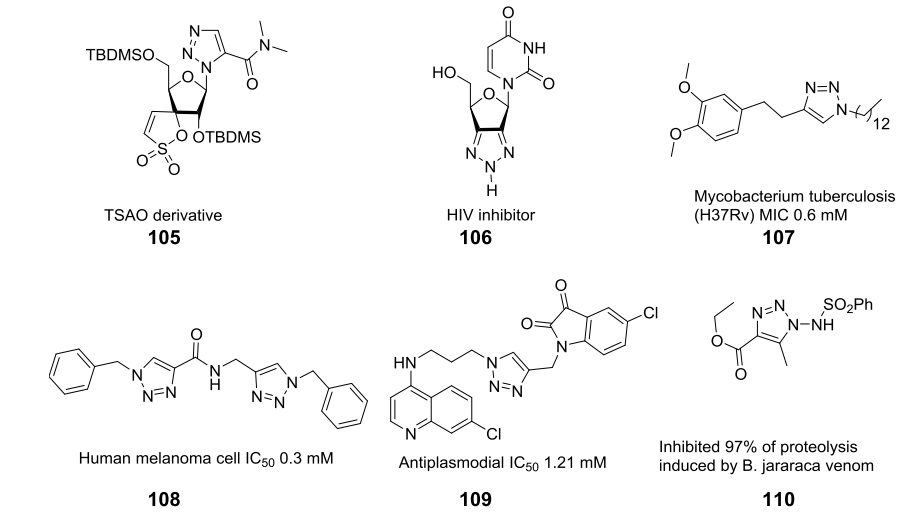


Scheme 21 synthesis of 1,4,5-trisubstituted 1,2,3-triazoles

1.3 Synthesis of bioactive triazole derivatives

According to a World Health Organisation survey in 2016, HIV has killed more than 36 million people worldwide and approximately 39 million people were infected by HIV. Thus, considering the risk of HIV, a vast number of studies has been done. However, there are limited number of reports on 1,2,3-triazoles derivatives having promising anti-HIV activity. For instance, the most important one is the 1,2,3-triazole derivative of tert-butyldimethylsilyl spiroamino-oxathioledioxide or TSAO, was reported in 1995 and tested against different HIV cell lines. The derivative **105** was found to be most active derivative of this triazole derivative series with anti-HIV-1 activity (50% effective concentration: 0.056-0.52 pM). [26]

Cancer is also a major fatal disease which causes the second most number of death after cardiovascular diseases. Recently, it has been discovered that artemisinin derivatives also possess anticancer activity combined with low toxicity. Among these, 11-aza-artemisinin and its derivatives were mostly studied and are known to possess various biological activities. However, the lack of an efficient functional handle for further diversification of aza-artemisinin limits its application in pharmaceutical chemistry.



Scheme 23 schematic diagram of compounds containing a triazole unit

Over the years, triazoles have been studied for various biological activities, including antibacterial, antiviral, antifungal, antieleptic, anti-alergic, antimicobacterial, anti-HIV (**106**), antimycobacterial (**107**), antimelanoma (**108**), antiplasmodial (**109**) and hemolysis (**110**) activities.[27-35]

Tazobactum (**111**), which is a commercial drug, is know for antibiotic activity. Furthermore, there are two drugs containing a triazole moiety in clinical trial such as carboxyamidotriazole (**112**) and cefatrizine (**113**) for anticancer activity.[35b]

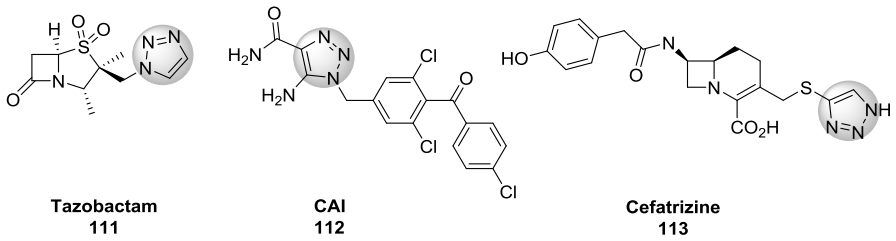
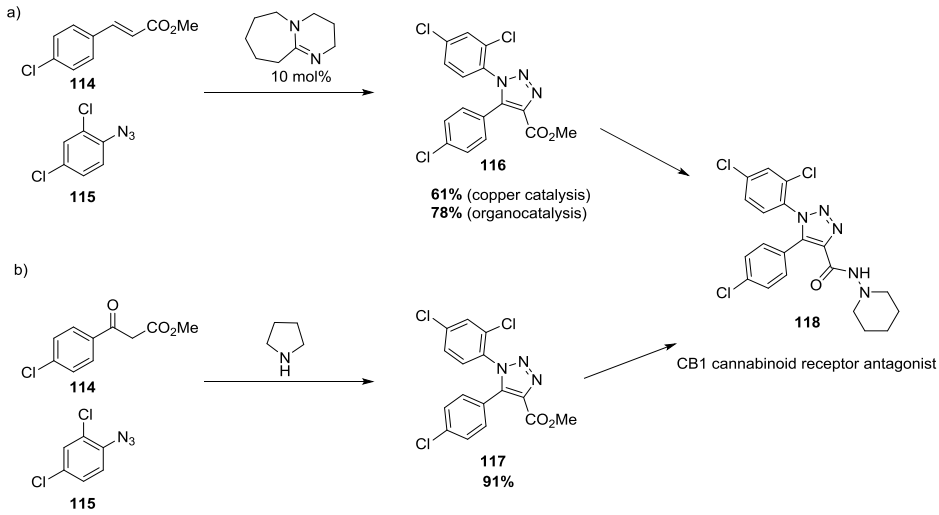


Figure 3 Drugs containing triazole

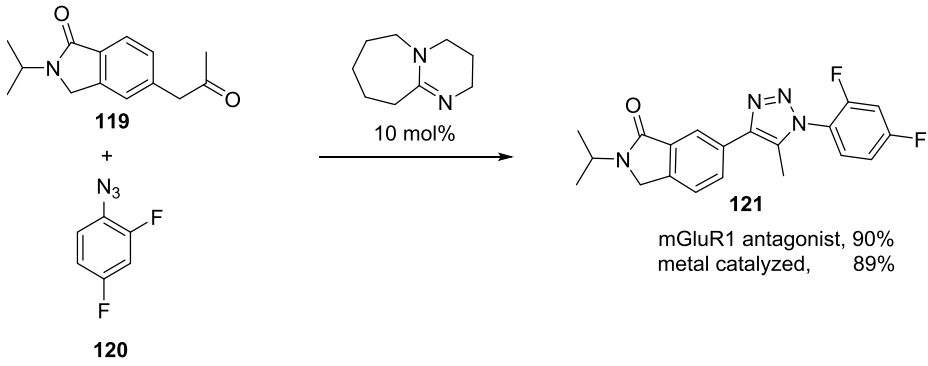
Because of the importance of triazole moieties, several synthetic strategies were discovered to access the triazole containing drug like molecules. In this section of the introduction we are going to present

only organocatalytic route towards the synthesis of drug or drug like molecules containing triazoles moieties. For instance, G protein-coupled cannabinoid receptor (CB1) agonists, with the receptor located primarily in the central and peripheral nervous system, are known as potent pharmacological agents in drug development for various diseases such as pain, glaucoma, nausea, cancer and Parkinson's disease. CB1 agonists **118** can be prepared in three steps *via* the copper-catalyzed azide-alkyne cycloaddition reaction in an overall yield 61% (Scheme 24).[36] However, recently, the group of Wang has reported a metal free method to access this type of agonist in a single step starting form α, β - unsaturated ester **114** and an azide **115**. The same group has also reported a series of cannabinoid receptors which are synthesized in one step.[37]



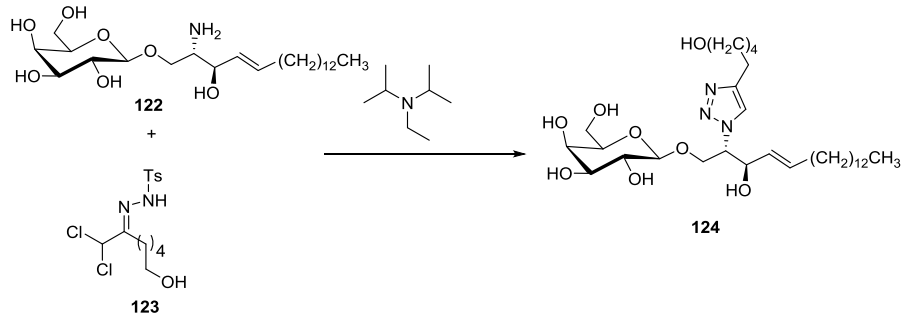
Scheme 24 synthesis of CB1 cannabinoid receptor antagonists

Recently, an efficient organocatalytic synthesis of mGluR1 antagonist **121** was reported by the Ramachary group starting from readily accessible starting materials such as enolizable ketone **119** and an azide **120** in a single step (Scheme 25).[38]



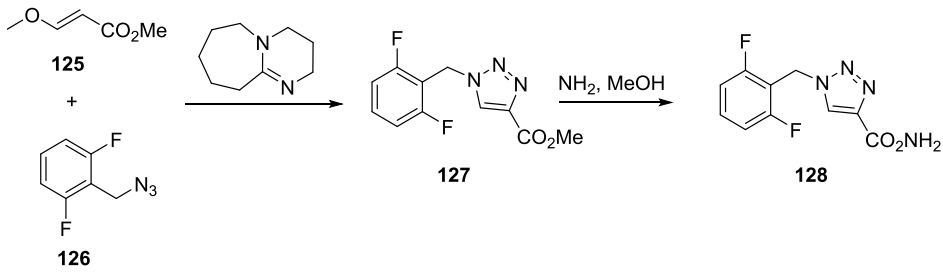
Scheme 25 synthesis of mGluR1 antagonist

Ceramides are known to cause apoptosis in the mammalian system. A series of ceramide analogs have been prepared *via* click reaction, there by replacing the amide bond with a triazole linkage.[39] An organocatalytic, single step approach towards triazole modified psychosine **124** has also been reported by Westermann in 2012 (Scheme **26**).



Scheme 26 synthesis of ceramide derivative

A two-step synthesis of the anticonvulsant drug rufinamide has been reported by Wang in 2015, where the first step consists of an organocatalytic triazole formation from an α,β - unsaturated ester **125** and an azide **126** in the presence of DBU as a catalyst. After an amidation reaction of **127**, rufinamide **128** was obtained in 89% overall yield.[40]



Scheme 27 synthesis of rufinamide

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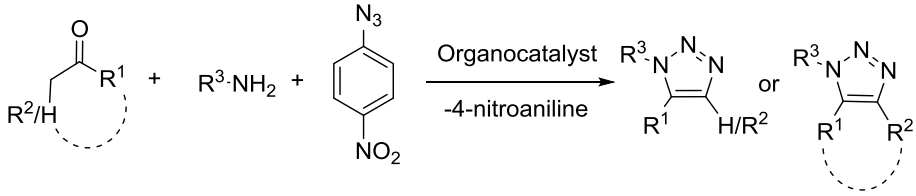
Goals and objectives

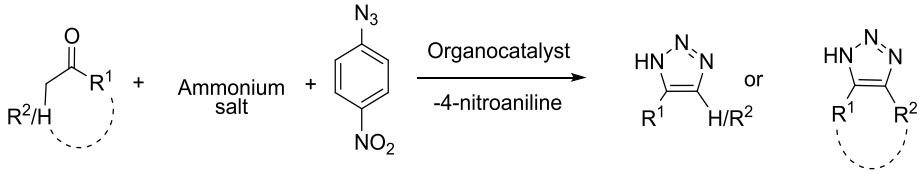
Considering the importance of triazoles in drug discovery, organic chemists are highly motivated to discover more efficient synthetic strategies to access complex drug like molecules bearing 1,2,3-triazole moiety. The research on triazole chemistry has been increased extensively after the discovery of regioselective 3+2 cycloaddition of alkynes and azides. Since then, a vast number of metal as well as organocatalytic methodology towards the synthesis of 1,2,3-triazoles has been reported. However, a general methodology is still lacking to access highly functionalized 1,2,3-triazoles. In the context of our ongoing projects concerning triazole chemistry, the main target of this research is to develop new methodologies towards the synthesis of trisubstituted 1,2,3-triazoles and their biological evaluation.

At the initial stage of this PhD thesis, we will investigate a three-component reaction of readily available starting materials such as enolizable ketones, primary amines, and para-nitrophenyl azide leading to trisubstituted triazoles. After successful investigation of this three-component reaction, we will study the scope and limitation of this reaction with variety of aromatic and aliphatic enolizable ketones. Next, we will investigate the reaction tolerance with various primary amines as well aromatic amine. In addition, we will investigate the formation of bis- and tris-1,2,3-triazoles by using this methodology. Furthermore, to fully exploit the versatility of this MCR, bioactive natural products containing functional groups such as primary amines and enolizable ketones will also be investigated to access novel and unique triazole-containing natural products.

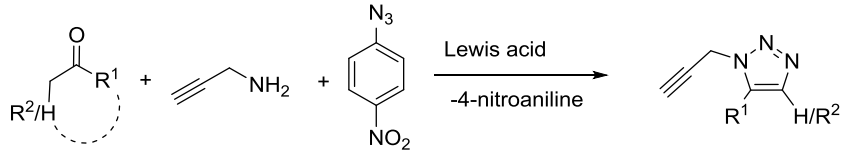


After successful investigation of multicomponent reaction towards trisubstituted 1,2,3-triazoles, we will focus on synthesizing *NH*-1,2,3-

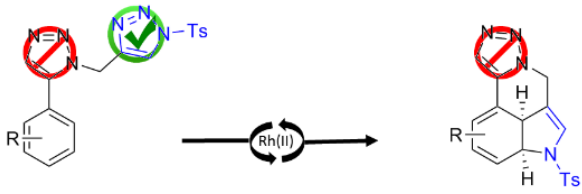
triazoles by replacing amine with various ammonium salt in the previous multicomponent reaction. After optimization of this reaction, we will investigate the feasibility of this reaction on various cyclic enolizable ketones to form 4,5-fused *NH*-triazoles. Furthermore, the regioselectivity of this reaction will be studied with unsymmetrical enolizable ketones. This novel triazolization strategy will provide a convenient gateway to synthesize high value *NH*-1,2,3-triazole derivatives which are known to be active pharmaceutical agents, or potential supramolecular receptors in a single step from simple and readily available building blocks.



Next part of this PhD study, we will elucidate a highly efficient and regiospecific lewis catalyst mediated synthesis of propargyl functionalized triazole derivatives in a single step from ketones and propargyl amine. After optimization of this reaction, we will explore the synthesis of 4,5-fused propargyl 1,2,3-triazoles starting from cyclic ketones. The regioselectivity of this reaction will also be investigated. This methodology will give access to a special type of propargyl substituted triazoles which are not possible to synthesize by other means. Furthermore, we will explore the functionalization of propargyl triazoles with azides *via* click reaction to form a unique type of *N*-*C* linked bis-triazoles.



Azavinylcarbenes derived from N-sulfonyl-1,2,3-triazoles have drawn considerable attention in the chemical community as a means towards the synthesis of various heterocycles. 1,2,3-Triazoles are known to be very stable heterocycles, however they can be decomposed to azavinylcarbenes by using appropriate substituents on the 1,2,3-triazole ring and a transition metal catalyst. A vast number of studies has been done on the synthesis of various heterocyclic compounds by using azavinylcarbene as a key intermediate. However, there are no report so far on the selective decomposition of triazoles in presense bis-triazoles. By using appropriate substitutents on *N-C* linked bis triazoles and appropriate meta catalyst, we will investigate the selective decomposition of triazoles which could lead to formation of 3,4-fused indoles. We will also investigate the feasibility of one pot synthesis starting from propargyl triazoles. In this one pot reaction, we will react propargyl triazole with tosyl azide to form *N-C* linked bis triazoles by using copper catalyst. The N-C linked bis-triaozoles can be decomposed in same pot by using rhodium catalyst with out purification of starting materials. Furhtermore, we will also study the oxidation of dihydro 3,4-fused indoles to corresponding fused indoles by using oxidative agents.



At the end of this PhD thesis, we will investigate the synthesis of various artemisinin derivatives of triazole. Artemisinin, which is a naturaly occouring 1,2,4-trioxane sesquiterpene, is well known to possess antimalarial activity. Recently, it has been discovered that artemisinin derivatives also possess anticancer as well as anti-viral activity with low toxicity. However, the wider application of artemisinin in drug discovery has been restricted due to the delicate structure of artemisinin. In this thesis, we will investigate the stability

of artemisinin in triazolization reactions. We will also explore and synthesize artemisinin derivatives of triazoles by using triazolization methodology. In addition, we will also investigate the activity of novel artemisinin derivatives in various cancer as well as virus strains.

Chapter 2

A general metal-free route towards the synthesis of 1,2,3-triazoles from readily available primary amines and ketones

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of 1,2,3-triazoles from readily available primary amines and ketones" Joice Thomas, Sampad Jana, Jubi John, Sandra Liekens and Wim Dehaen Chem. Commun., 2016,52, 2885-2888] Copyright © [2016] Royal Society of chemistry.
Joice Thomas carried out the experiments, analyzed the data and wrote manuscript, Sampad Jana carried out the experiments and analyzed the data.

2.1 Introduction

In recent years, 1,2,3-triazole-containing molecules have received attention in diverse fields.[1] Currently, the most publicized ways to access 1,4- and 1,5-disubstituted 1,2,3-triazoles are the Cu- and Ru-catalyzed azide–alkyne cycloaddition reactions, respectively.[2] However, the limited access to terminal alkynes and the toxicity of the heavy metal catalysts hamper a wider exploration.[3] Several metal-free methods have been developed for the regioselective synthesis of 1,4-disubstituted 1,2,3-triazoles.[4] Nevertheless, selective pathways towards 1,5-disubstituted triazoles are rather scarce.[5] It is well documented that the cis-locked geometry present in 1,5-disubstituted triazoles could be an advantage to increase the biological activity and binding affinity towards several biological targets.[6] Unfortunately, the lack of an efficient and very general synthetic route to achieve a diverse library of these isomers limits their applications in medicinal chemistry.[6c] More recently, significant attention has been given to the preparation of diversely functionalized 1,2,3-triazoles via organocatalysis rather than metal catalyzed routes.[7,8] Unfortunately, the scope of these reactions is mostly limited to aromatic groups at the N1-position of the triazole heterocycles and extension to aliphatic substituents is cumbersome. Moreover, most transformations reported so far relied on organic azides that are mostly non-commercial and potentially hazardous. Other major limitations are the low substrate scope of the other component with reactivity limited mostly to activated carbonyl compounds. A very general and metal-free procedure to synthesize 1,5-disubstituted 1,2,3-triazoles is still lacking. Also, none of these methodologies have yet been applied to synthesize triazole derivatives of readily available natural products which could for instance facilitate structure activity relationship studies of bioactive/drug-like molecules.

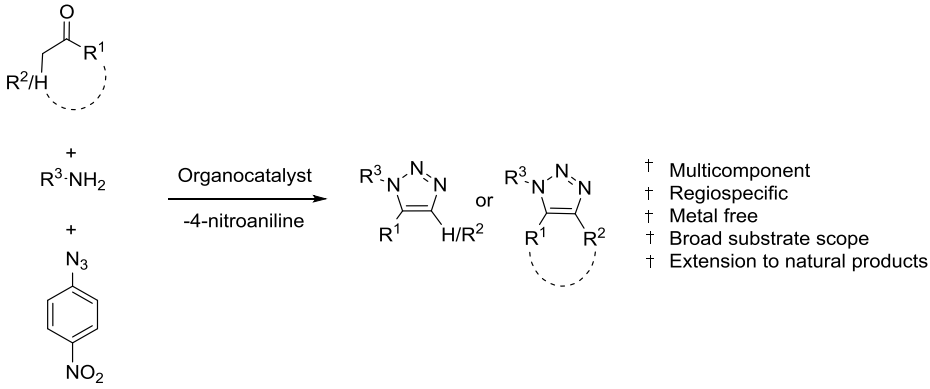
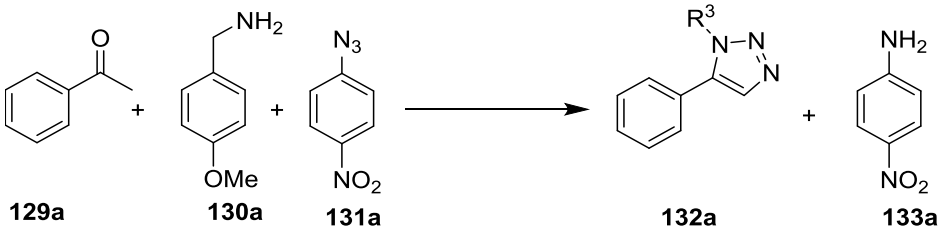


Figure 4 Multicomponent reaction towards functionalized 1,2,3-triazoles.

2.2 Result and discussion

In 1965, Pocar *et al.* described the reaction of an isolated imine/enamine (derived from acetone and propylamine) with 4-nitrophenyl azide (**131a**) which yielded 1-propyl-5-methyl-1,2,3-triazole in moderate yield.[9a] Surprisingly, this report remained virtually unnoticed, and no further attempts were made towards the further development of this protocol. One of the central challenges that could be associated with this method is the reversibility of the imine/enamine formation, hampering its isolation. This led us to the design of a multicomponent reaction starting from an enolizable ketone, primary amine and **131a**. We surmised that both the imine formation and the isomerization of enamine can be accelerated by a catalytic amount of an organic acid. The reaction would proceed via a sequence of (a) Schiff base formation, (b) tautomerisation of the enamine, (c) 3+2 cycloaddition reaction with **131a**, and (d) aromatization with the loss of 4-nitroaniline (**133a**). Such a cascade process that combines multiple individual transformations in one operation is particularly attractive in triazole synthesis because isolation of the intermediate species, which may be difficult and time consuming especially when large collections of compounds are required, is avoided. Moreover, amines and ketones are inexpensive and abundantly present in biologically active natural products. Even

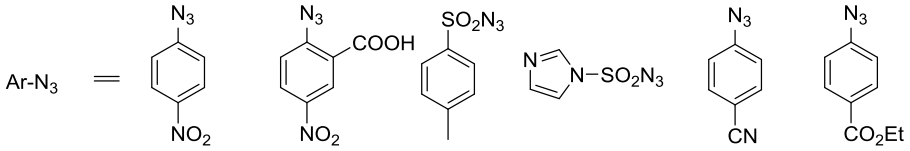
more alluring is that this could lead to previously inaccessible 1,5-disubstitued 1,2,3-triazoles via a metal-free pathway.



129a **130a** **131a** **132a** **133a**

Entry	Ratio **129a:130a:131b**	Catalyst (mol%)	Ar-N_3	Solvent	isolated Yield[b]
1	1:1:1	TsOH (20)	**131a**	toluene	80
2	1:1:1	TsOH (20)	**131b**	toluene	25
3	1:1:1	TsOH (20)	**131c**	toluene	trace
4	1:1:1	TsOH (20)	**131d**	toluene	trace
5	1:1:1	CF_3COOH (20)	**131a**	toluene	81
6	1:1:1	NEt_3: TsOH (20)	**131a**	toluene	83
7	1:1:1	CH_3COOH (20)	**131a**	toluene	84
8	1:1.2:1	CH_3COOH (20)	**131a**	toluene	86
9	1:1.4:1	CH_3COOH (20)	**131a**	toluene	90
10c	1:1.4:1	CH_3COOH (30)	**131a**	toluene	93
11	1:1.4:1	CH_3COOH (30)	**131a**	toluene	90
12	1:1.4:1	L-proline (30)	**131a**	toluene	62
13	1:1.4:1	Morpholine:TsOH (30)	**131a**	toluene	62
14[d]	1:1.4:1	CH_3COOH (30)	**131e**	toluene	65
15[e]	1:1.4:1	CH_3COOH (30	**131f**	toluene	43
16	1:1.4:1	none	**131a**	toluene	71
17[f]	1:1.4:1	none	**131a**	toluene	85
18	1:1.4:1	CH_3COOH (30)	**131a**	CH_3CN	85
19	1:1.4:1	CH_3COOH (30)	**131a**	THF	70

20	1:1.4:1	CH_3COOH (30)	**131a**	$ClCH_2CH_2Cl$	56
21	1:1.4:1	CH_3COOH (30)	**131a**	DMSO	78
22	1:1.4:1	CH_3COOH (30)	**131a**	DMF	67
23	1:1.4:1	CH_3COOH (30)	**131a**	EtOH	74
24	1:1.4:1	CH_3COOH (30)	**131a**	1,4-dioxane	80



131a **131b** **131c** **131d** **131e** **131f**

Table 1 Optimization of reaction conditions for the organocatalyzed three-component reaction of acetophenone (**129a**), 4-methoxybenzylamine (**130b**) and organic azides (**131a**-**d**)

[a] Reaction conditions: except where otherwise noted, **129a** is always in 0.42 mmol amount and the molar ratio of **130a** and **131a** is calculated on the basis of this, reaction temperature is 100°C, solvent (0.4 mL, 1 molar), 4 Å molecular sieves (30 mg) and reaction time is 12 h. [b] isolated yield after column chromatography. [c] reaction performed without molecular sieves and reaction time is 20 h. [d] reaction time is 40 h. [e] reaction time is 56 h. [f] reaction time is 24 h. TsOH is p-toluenesulfonic acid.

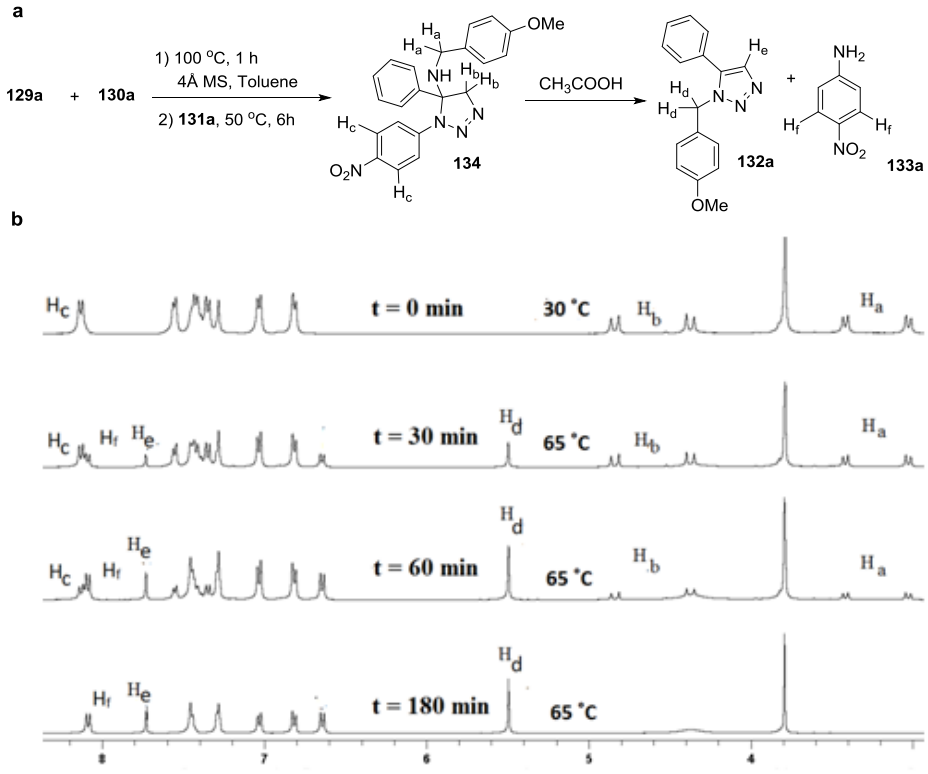
In order to validate this synthetic design, we have chosen acetophenone (**129a**), 4-methoxybenzylamine (**130a**) and **131a** as model substrates. We started to investigate the optimization of reaction conditions by selecting acetophenone (**129a**) and 4-methoxybenzylamine (**130a**) as the model reagents with various diazo transfer reagents, catalysts and solvents to form 1,5-disubstituted triazole **132a** as summarized in Table 1. We presumed that the addition of 4 Å molecular sieves favors imine formation by effectively removing water from the carbonyl + amine imine + H_2O equilibrium. Initial experiments were conducted via a MCR of these reagents in the presence of 4-nitrophenyl azide (**131a**) as the diazo-transfer reagent and 30 mol% of p-toluenesulfonic acid (TsOH) as the catalyst over 4 Å molecular sieves in toluene (0.4 mL, 1 molar) at 100 °C in a sealed tube

for 12 h (Table 1, entry 1). To our delight, this combination promoted the reaction with an excellent of yield of 80%. The use of **131b** as diazo transfer agent resulted in a significant reduction in the yield of the title compound **132a** to 25% (Table 1, entry 2). Subsequently, performing the reaction with other azido compounds that are known as diazo transfer reagents, such as **131c** and **131d** resulted in much lower efficiencies (Table 1, entries 3 & 4). One possible reason for this is the formation of corresponding sulfonamide as a side product which derived from the nucleophilic substitution reaction of **130a** with **131c** and **131d**. Interestingly, among the different Bronsted acid catalysts tried, CH_3COOH gave the best result (Table 1, entries 5-7). We then examined various stoichiometries of the building blocks and different loading of CH_3COOH catalyst on the reaction performance (Table 1, entries 8-10). The best result was obtained while using 1.4 equivalents of **130a** and 30 mol% of CH_3COOH catalyst, and the desired three-component-coupling product **132a** was obtained in 93% yield (Table 1, entries 10).

When performing the reactions with secondary amine catalysts such as L-proline and morpholine:p-toluenesulfonic acid salt, however, lower yields were obtained (Table 1, entry 12 and 13). Next, we performed the reaction with other azido compounds analogous to **131a** such as 4 azidobenzonitrile **131e** (Table 1, entry 14) and ethyl 4-azidobenzoate (Table 1, entry 15) **131f**. These reactions of less electron poor aryl azides were less efficient than the ones performed with **131a** and also required longer reaction times for the complete consumption of the starting materials. Remarkably, this reaction also worked fine under acid free conditions without significantly affecting the yield of **132a** (85%) although the required reaction time was longer (24 h) (Table 1, entry 17). This observation can be viewed as an additional advantage as this transformation could also be extended to acid sensitive substrates. The yields of the reactions are also influenced by the solvent (Table 1, entries 18-24): MeCN (85%), THF (70%), $ClCH_2CH_2Cl$ (56%), DMSO (78%), DMF (67%), EtOH (74%), 1,4-dioxane (57%). Therefore, a three-component reaction of **129a**, **130a** and **131a** in a respective molar ratio of 1:1.4:1.1 using 30 mol% of acetic acid (8 mg, 0.13 mmol) as catalyst over 4 Å molecular sieves in

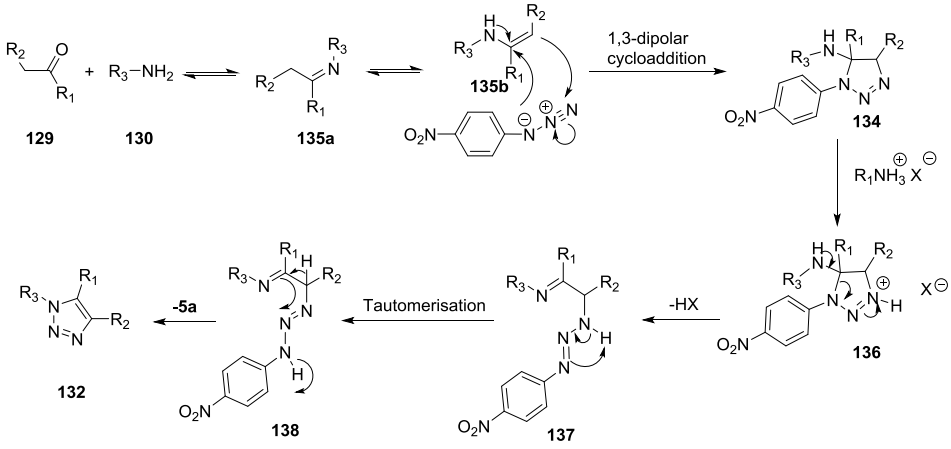
1 molar solution of toluene at 100 °C in a sealed tube under argon atmosphere over a period of 12 h proved to be the conditions of choice After some optimization, we found that for the three-component reaction of **129a**, **130a** and **131a** in a respective molar ratio of 1:1.4:1 using 30 mol% of acetic acid as a catalyst over 4 Å molecular sieves in 1 M solution of toluene at 100 ^{o}C was the reaction condition of choice. The desired product **132a** was obtained after 12 h with an isolated yield of 93%. As expected, quantitative conversion of **131a** to **133a** was also observed.

We conducted several control experiments to understand the mechanism of the reaction. For instance, two separate experiments were conducted and monitored by ^{1}H NMR spectroscopy, with the isolated adduct **134** and 1**31a** in the presence and absence of the catalyst in $CHCl_3$ at 65 °C in an NMR tube (Scheme 28). Interestingly, the reaction in the presence of acid was complete after 3 hours and exclusively yielded the expected products **132a** and **133a** in 1:1 ratio, presumably as a result of protonation of the N-3 of the aminotriazoline intermediate **134** followed by a ring opening/ring closure sequence (Scheme 28a). On the other hand, in the case of acid-free conditions, the reaction proceeded very slowly and complete conversion at 65°C was observed only after 40 hours. Furthermore, we monitored a one-pot reaction starting from **129a**, **130a** and 1**31a** under acidic conditions (30% AcOH) at 65°C and the reaction was finished only after 48 hours. This observation convincingly demonstrated that the Schiff base formation is slow at this temperature. Taken together, the results of these experiments are in agreement with the hypothesis that imine/enamine formation is the rate determining step. We presume that the imine/enamine species is in equilibrium with the starting material **129a** and **130a**, and the formation of the key intermediate **134** from a 3+2 cycloaddition reaction between transiently generated enamine and **131a** displaces this equilibrium (Scheme 29).



Scheme 28 Proposed mechanistic experiments and catalytic cycles

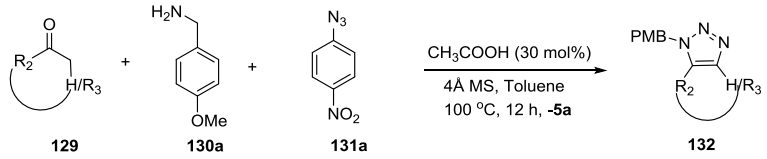
[a] Scheme showing the synthesis of the triazoline intermediate **134** and its subsequent conversion to **132a** and **133a**. [b] The ^{1}H NMR spectra showing the clean formation of the triazole **132a** and **133a** upon heating the triazoline intermediate **134** in presence of 8 mol% of CH_3COOH in $CDCl_3$ at 65 °C.



Scheme 29 Postulated mechanism.

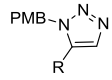
With this newly developed metal-free three-component protocol we first set out to survey the scope and limitations of this methodology with a variety of aromatic and aliphatic enolizable ketones. Acetophenones with both electron-donating and electronwithdrawing groups smoothly underwent these transformations (**132a–132i**) (Table 2a). To our delight, various interesting heterocyclic moieties were amenable to the reaction providing access to triazole derivatives which are otherwise difficult to synthesize (**132l–132n**). The utility of this reaction was further demonstrated by the transformation of acetyl ferrocene and 6-acetyl uracil. It is worth mentioning that these reactions failed in an acidic environment but fortunately under acid-free conditions the expected products **132o** and **132p** were obtained in good yields. Next, we investigated the scope of this reaction towards the synthesis of 1,4,5-trisubstituted 1,2,3-triazoles (Table 2b). For instance, aryl or alkyl ketone precursors such as aryl propanones or 5-nonanone lead to the expected trisubstituted triazoles in excellent yield (**132q–132t**). However, the extension of this reaction to activated methylene ketones such as ethyl benzoylacetate leads to the well-known Dimroth product formed by the 3+2 cycloaddition of **132a** with either the enolate or enamine intermediate.[10] An initial investigation with an unsymmetrical ketone, for example 2-butanone, gave mostly the expected product **132u** together with a noticeable amount of 18%

of the other regioisomer **132v** (Table 2c). In light of these results, we reasoned that during the course of the reaction an equilibrium mixture of the two enamines will form and the composition of this is in favor of the most substituted enamine. This eventually gives **132u** as the major isomer. On the other hand, the ease of attack onto the less hindered enamine leads to a minor amount of the kinetic product **132v**. Interestingly, methyl isopropyl ketone led to 10% of the stable triazoline intermediate **134w** derived from the more substituted enamine together with 56% of the kinetic product **132w**. We then examined the scope of this reaction with respect to different cyclic ketones (Table 2d). The synthesis of N1-alkyl derivatives of carbo- as well as O- and N-heterocyclic fused triazole derivatives is scarcely reported (**132x–132ab**). Additionally, different aromatic bicyclic ketones were also compatible with the reaction (**132ac–132ag**). The high regioselectivity obtained with 2-tetralone shows that cycloaddition occurs with the most stable enamine, thus yielding **132ag** as the sole product.

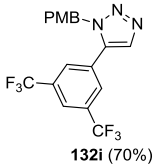


129 **130a** **131a** **132**

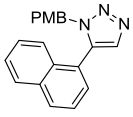
a) 1,5-Disubstituted 1,2,3-triazoles



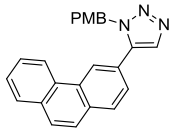
132a (93%), R = Ph
132b (89%), R = *p*-OMe-Ph
132c (68%))[b], R = *p*-NH_2-Ph
132d (88%), R = *o*-Me-Ph
132e (79%), R = *p*-Cl-Ph
132f (62%)[b], R = *p*-NO_2-Ph
132g (62%))[c], R= CH_3
132h (83%), R = *t*-Bu



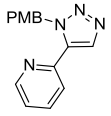
132i (70%)



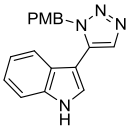
132j (80%)



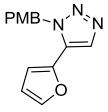
132k (91%)



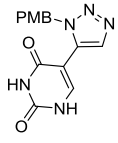
132l (82%)[d]



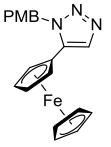
132m (83%)



132n (68%)[d]

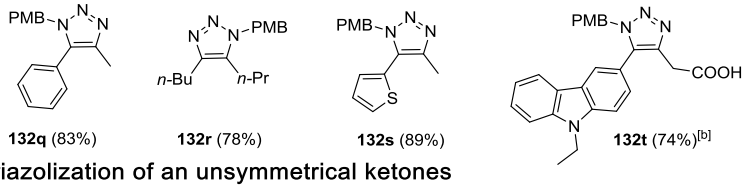


132o(67%)[e]



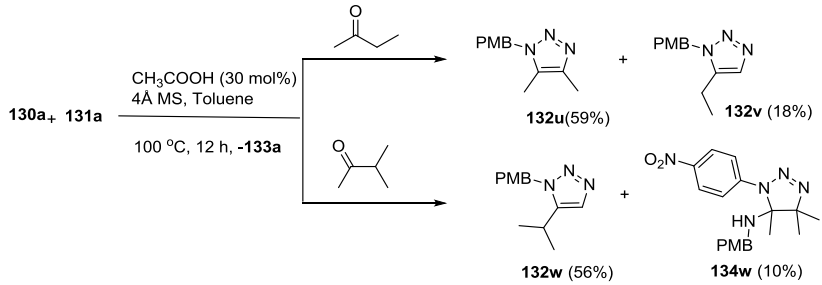
132p (79%)[f]

b) 1,4,5-Trisubstituted 1,2,3-triazoles



132q (83%) **132r** (78%) **132s** (89%) **132t** (74%)[b]

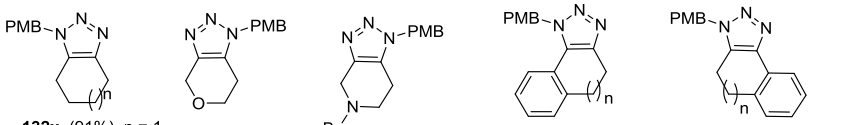
c) Triazolization of an unsymmetrical ketones



130a+ **131a**

132u(59%) **132v** (18%) **132w** (56%) **134w** (10%)

d) 4,5-Fused 1,2,3-triazoles



132x (91%), n = 1
132y (89%), n = 3
132z (95%), n =7

132aa (76%)[d] **132ab** (73%)[d]

132ac (95%), n = 0
132ad (85%), n = 1
132ae (94%), n = 2

132af (75%), n = 0
132ag (82%), n = 1

Table 2 substrate scope with respect to ketones

[a] Reaction conditions: **129** (1 equiv.), **130a** (1.3 equiv.), **131a** (1.0 equiv.), CH_3COOH (30 mol%), toluene (0.4 mL), 100 °C, 12 h, Isolated yield. [b] 40 h. [c] 3 equivalent of **129g**. [d] CH_3COOH (0 mol%), 24 h. [e] CH_3COOH (0 mol%), DMF (0.6mL), 12 h. [f] Reaction Conditions: **129p** (1 equiv.), **130a** (2.8 equiv.), **131a** (2.0 equiv.), toluene (1.5 mL), 100 °C, 72 h. [e] 24 h.

In a next series of experiments the substitution pattern in the amine part was varied (**132ah–132aq**). More importantly, substrates bearing unprotected secondary amines such as **132ak** and **132al** could be effectively transformed using the current conditions. Remarkable functional group tolerance was observed in the case of allyl amine and 2,2-dimethoxyethylamine where the alkene and acetal functionalities remained intact under acid-free conditions (**132am** & **132an**). This elegant strategy was also applied to synthesize chiral-unit-containing triazoles by using different chiral amines (**132ao** & **132ap**). As

expected, the extension of our protocol to aromatic amines gave a dissatisfactory yield of only 25% (**132aq**) caused by the lower reactivity of the intermediate enamines. However, the N-aryl triazoles are easily obtained by other methods (Table 3).[5,7,8]

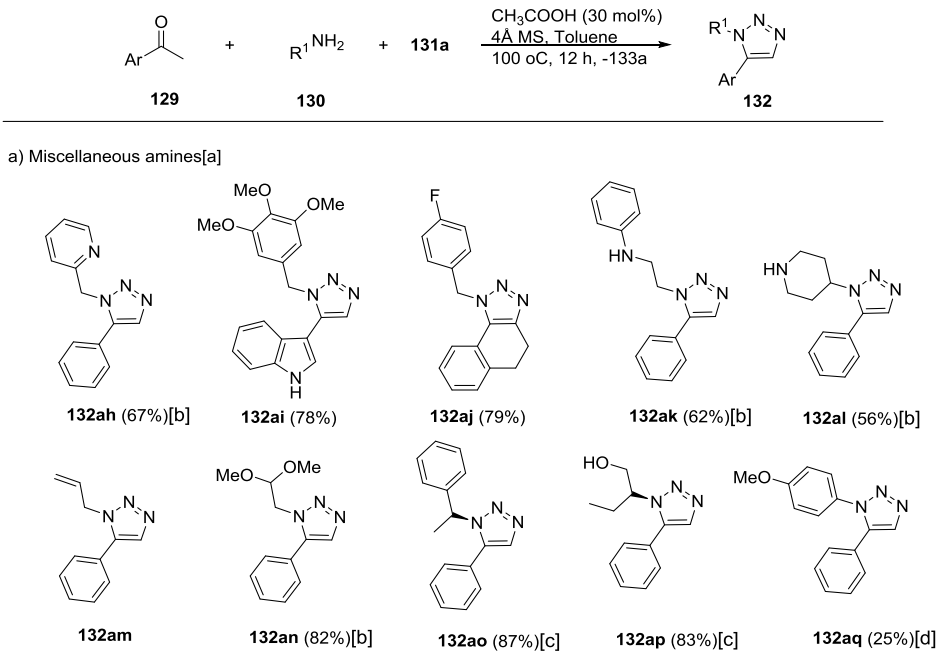
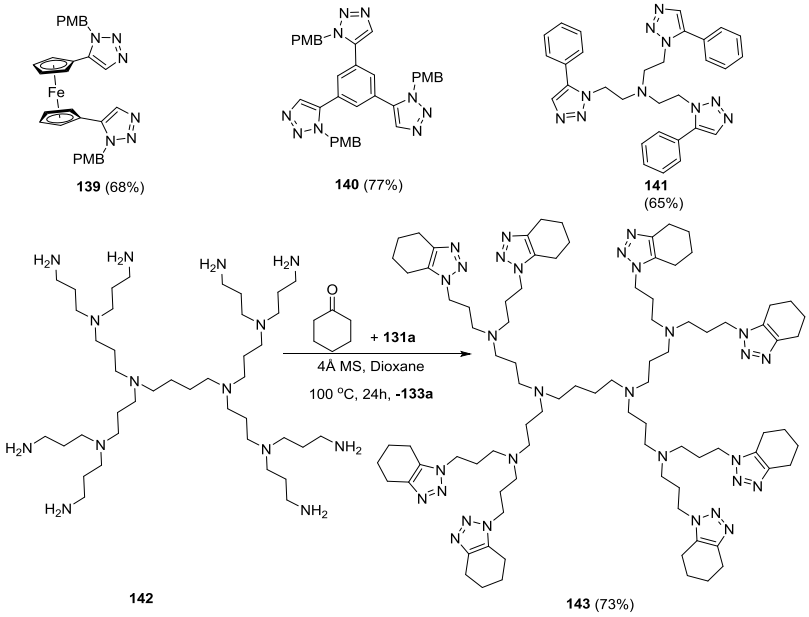


Table 3 Substrate scope with respect to amines

[a] Reaction conditions: **129** (1 equiv.), **130a** (1.3 equiv.), **131a** (1.0 equiv.), CH_3COOH (30 mol%), toluene (0.4 mL), 100 ^oC, 12 h, Isolated yield. [b] CH_3COOH (0 mol%), 24 h. [c] 48 h, CH_3COOH (30 mol%). [d] 48 h. [e] **129** (1 equiv.), **130** (2 equiv.), **131a** (1.0 equiv.), CH_3COOH (0 mol%), toluene (0.6 mL), 100 ^oC, 48 h.

To demonstrate the utility of this reaction in material science, novel oligotriazole derivatives **139** & **140** derived from bi/tri-acetyl compounds could be generated in good yields after multiple MCRs without being affected by any steric hindrance (Scheme 30). Polymeric or dendritic triazole materials are of current interest.[1] The need for building blocks having multiple azide groups may be a limiting factor since they are potentially shock-sensitive compounds.[11] We surmised

that the present approach is a safer alternative. Accordingly, readily available tris(2-aminoethyl)amine was subjected to reaction conditions to afford the C3-symmetric derivative **141** in good yield. To further demonstrate the utility of this approach to dendrimer chemistry, the modification of the 2nd generation dendron **142** with cyclohexanone was considered. Clean conversion to a monodisperse fused polytriazole amine **143** in reasonable yield was observed.



Scheme 30 Substrate scope of the various multifunctional building blocks

To fully exploit the versatility of this MCR, bioactive natural products containing functional groups such as primary amines and enolizable ketones were investigated to access novel and unique triazole-containing natural products which are expected to enable SAR studies facilitating subsequent drug developments for human diseases (Table 4). The application of the triazolation conditions to histamine **144a** and tryptamine **144b** led to the expected 1,5-disubstituted 1,2,3-triazoles in reasonable yields (**145a** and **145b**). Leelamine **144c** (an optically active diterpene amine which binds weakly to human cannabinoid receptors) was also structurally modified to new triazole entities

145c.[12] Additionally sphingoid base, phytosphingosine **144d**, was easily modified to non-hydrolysable ceramide analogue **145d** (the amide bond of ceramide was replaced by bioisosteric 1,2,3-triazole functionality) in a single step without performing a laborious protection/ deprotection strategy.[13] Several D-ring tethered heterocyclic compounds of estrone **144e** were identified as useful templates for the design of inhibitors of steroidogenic enzymes such as 17β-hydroxysteroid dehydrogenases.[14] This inspired us to synthesize estrone 16,17-fused 1,2,3-triazole derivatives **145e1** and **145e2** via this strategy using slightly modified reaction circumstances to surpass the steric effects of the reactants. As expected, the less sterically hindered butylamine gave a better conversion as compared to **130a**. The male hormone analogue, dihydrotestosterone **144f** gave excellent regio-selective triazolization on the A-ring leading to **145f** as a single product in 88% isolated yield.

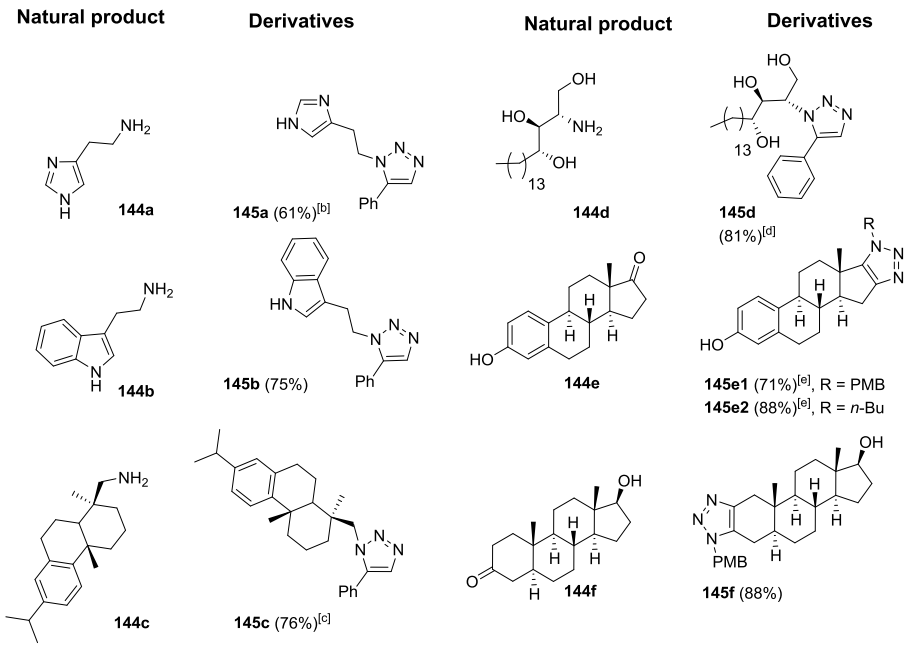


Table 4 Scope with respect to natural products

[a] Reaction Conditions: **129** (1 equiv.), **130a** (1.3 equiv.), **131a** (1.0 equiv.), CH_3COOH (30 mol%), toluene (0.4 mL), 100 °C, 12 h, Isolated yield. [b]

CH_3COOH (0 mol%), 24 h. [c] 48 h. [d] CH_3COOH (0 mol%), 48h. [e] **144e** (1 equiv.), **130** (2.8 equiv.), **131a** (2.0 equiv.), CH_3COOH (30 mol%), toluene (1 mL), 100 ^oC, 72 h. [f] DMF (0.6mL), 24 h.

2.3 Conclusion

In conclusion, we have developed a universal approach to access 1,2,3-triazole derivatives in a single step from simple and readily available enolizable carbonyl compounds and amines which could be considered not as the end point, but as the initial point for the rapid generation of complex triazole derivatives that are inaccessible by other means. In contrast to other well-established 1,5- or fused triazole syntheses where different organic azides that are non-commercial and potentially dangerous are used to bring diversity, this strategy makes use of a readily available organic azide and readily available aliphatic amines as the sources of nitrogen of the triazole heterocycles. We successfully illustrated the utility of this reaction in natural products by systematically transforming them into diverse triazole derivatives. The fifty-five examples of this unprecedented triazole synthesis show the scope and limitations of this strategy.

2.4 Experimental and Characterization data

2.4.1 Experimental Procedures

2.4.1.1 Preparation of 4-nitrophenyl azide (131a):

4-Nitroaniline (28.0 g, 0.20 mol) was suspended in 2.4 N HCl solution (300 mL) and methanol (60 mL) was added to aid the solubility. After cooling the solution to 0 °C, $NaNO_2$ (6 M, 40 mL) in water was added dropwise. The mixture was stirred at 0 °C for 30 minutes, after which a solution of NaN_3 (4.1 M, 60 mL) in water was added dropwise over 20 minutes and the whole reaction mixture was stirred for an hour at room temperature. The reaction mixture was extracted with diethyl ether and the organic fraction was washed with a saturated $NaHCO_3$ solution and brine, dried over $MgSO_4$ and concentrated under reduced pressure affording the pure compound **131a** as a yellow solid in 95%

yield (31.48 g). Spectroscopic data for **131a** was consistent with previously reported data for this compound.

2.4.1.2 General procedure for the preparation of substituted 1,2,3-triazoles

To an oven-dried screw-capped reaction tube equipped with a magnetic stirring bar was added the ketone, amine, 4-nitrophenyl azide (**131a**), acetic acid (0-30 mol%) and 4 Å molecular sieves (50 mg). The mixture was dissolved in the proper solvent and stirred at 100 °C for 12-72 hours. The crude reaction mixture was then directly purified by column chromatography (silica gel) at first with DCM as eluent to remove all 4-nitroaniline formed during the reaction followed by using a mixture of heptane and ethyl acetate as eluent to afford the corresponding 1,2,3-triazoles as off-white solids or semi-solids.

2.4.2 Characterization data

1-(4-Methoxybenzyl)-5-phenyl-1*H*-1,2,3-triazole (132a): Acetophenone (50 mg, 0.42 mmol), 4- methoxybenzylamine (80 mg, 0.58 mmol), 4-nitrophenyl azide (68 mg, 0.42 mmol), acetic acid (8 mg, 0.13 mmol), 4 Å molecular sieves (50 mg) and toluene (0.4 mL). Reaction time is 12 h. The product was purified by flash column chromatography (DCM followed by heptane/EtOAc = 6:4) affording **132a** (103 mg, 93% yield) as an off white semi-solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.45 - 7.42 (m, 3H), 7.28 - 7.25 (m, 2H), 7.01 (d, 2H, J = 8.6 Hz), 6.79 (d, 2H, J = 8.7 Hz), 5.48 (s, 2H), 3.78 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 138.1, 133.4, 129.6, 129.1, 129.0, 128.8, 127.6, 127.1, 114.3, 55.4, 51.5; MS (EI): m/z: 265 (M^+); HRMS (ESI+): m/z calcd for $C_{16}H_{16}N_3O$ $[M+H]^+$: 266.1287, found 266.1284.

1-(4-Methoxybenzyl)-5-(4-methoxyphenyl)-1*H*-1,2,3-triazole (132b): 4-Methoxy acetophenone (63 mg, 0.42 mmol), 4-methoxybenzylamine (80 mg, 0.58 mmol), 4-nitrophenyl azide (68 mg, 0.42 mmol), acetic acid (8 mg, 0.13 mmol), 4 Å molecular sieves (50 mg) and toluene (0.4 mL). Reaction time is 12 h. The product was purified by flash column chromatography (DCM followed by

heptane/EtOAc = 6:4) affording **132b** (110 mg, 89% yield) as an off white semi-solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (s, 1H), 7.18 (d, 2H, J = 8.5 Hz), 7.03 (d, 2H, J = 8.5 Hz), 6.94 (d, 2H, J = 8.6 Hz), 6.81 (d, 2H, J = 8.6 Hz), 5.45 (s, 2H), 3.85 (s, 3H), 3.78 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.6, 159.5, 137.8, 133.1, 130.4, 128.7, 127.8, 119.2, 114.5, 114.2, 55.5, 55.3, 51.3; MS (EI): m/z: 295 (M^+); HRMS (ESI+): m/z calcd for $C_{17}H_{18}N_3O_2$ $[M+H]^+$: 296.1393, found 296.1399.

4-(1- (4-Methoxybenzyl)-1*H*-1,2,3-triazol-5-yl)aniline (132c): 4-Aminoacetophenone (56 mg, 0.42 mmol), 4-methoxybenzylamine (80 mg, 0.58 mmol), 4-nitrophenyl azide (68 mg, 0.42 mmol), acetic acid (8 mg, 0.13 mmol), 4 Å molecular sieves (50 mg) and toluene (0.4 mL). Reaction time is 40 h. The product was purified by flash column chromatography (DCM followed by heptane/EtOAc = 4:6) affording **132c** (79 mg, 68% yield) as an off white semi-solid. ^{1}H NMR (300 MHz, CDCl3) δ 7.64 (s, 1H), 7.06 - 7.03 (m, 4H), 6.81 (d, 2H, J = 8.2 Hz), 6.69 (d, 2H, J = 7.9 Hz), 5.44 (s, 2H), 3.89 (sbr, 1H), 3.78 (s, 3H); 13C NMR (125 MHz, CDCl3) δ 159.5, 147.7, 138.4, 132.9, 130.2, 128.8, 128.0, 116.5, 115.1, 114.2, 55.4, 51.2; MS (EI): m/z: 280 (M+); HRMS (ESI+): m/z calcd for C16H17N4O $[M+H]^+$: 281.1397, found 281.1396.

1-(4-Methoxybenzyl)-5-(o-tolyl)-1*H*-1,2,3-triazole (132d): 2-Methylacetophenone (56 mg, 0.42 mmol), 4-methoxybenzylamine (80 mg, 0.58 mmol), 4-nitrophenyl azide (68 mg, 0.42 mmol), acetic acid (8 mg, 0.13 mmol), 4 Å molecular sieves (50 mg) and toluene (0.4 mL). Reaction time is 12 h. The product was purified by flash column chromatography (DCM followed by heptane/EtOAc = 6:4) affording **132d** (103 mg, 88% yield) as an off white semi-solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.40 - 7.35 (m, 1H), 7.23 (d, 2H, J = 7.0 Hz), 7.04 (d, 1H, J = 7.5 Hz), 6.87 (d, 2H, J = 8.95 Hz), 6.71 (d, 2H, J = 8.74 Hz), 5.27 (s, 2H), 3.75 (s, 3H), 1.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.60, 138.1, 136.5, 133.9, 130.5, 130.0, 129.5, 127.1, 126.7, 126.0, 114.0, 55.4, 51.6, 19.7; MS (EI): m/z: 279 (M^+); HRMS (ESI+): m/z calcd for $C_{17}H_{18}N_3O$ $[M+H]^+$: 280.1444, found 280.1445.

5-(4-Chlorophenyl)-1-(4-methoxybenzyl)-1*H*-1,2,3-triazole (132e): 4-Chloroacetophenone (64 mg, 0.42 mmol), 4-methoxybenzylamine (80 mg, 0.58 mmol), 4-nitrophenyl azide (68 mg, 0.42 mmol), acetic acid (8 mg, 0.13 mmol), 4 Å molecular sieves (50 mg) and toluene (0.4 mL). Reaction time is 12 h. The product was purified by flash column chromatography (DCM followed by heptane/EtOAc = 6:4) affording **132e** (98 mg, 79% yield) as an off-white solid. m.p. 56 - 57 ˚C. ^{1}H NMR (300 MHz, CDCl3) δ 7.71 (s, 1H), 7.40 (d, 2H, J = 8.1 Hz), 7.18 (d, 2H, J = 8.5 Hz), 6.91 (d, 2H, J = 8.6 Hz), 6.80 (d, 2H, J = 8.7 Hz), 5.46 (s, 2H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, CDCl3) δ 159.7, 136.9, 135.9, 133.6, 130.4, 129.3, 128.7, 127.4, 125.6, 114.4, 55.4, 51.6; MS (EI): m/z: 299 (M^+); HRMS (ESI+): m/z calcd for $C_{16}H_{16}ClN_4O$ $[M+H]^+$: 300.0899, found 300.0896.

1-(4-Methoxybenzyl)-5-(4-nitrophenyl)-1*H*-1,2,3-triazole (132f): 4-Nitroacetophenone (69 mg, 0.42 mmol), 4-methoxybenzylamine (80 mg, 0.58 mmol), 4-nitrophenyl azide (68 mg, 0.42 mmol), acetic acid (8 mg, 0.13 mmol), 4 Å molecular sieves (50 mg) and toluene (0.4 mL). Reaction time is 40 h. The product was purified by flash column chromatography (DCM followed by heptane/EtOAc = 6:4) affording **132f** (80 mg, 62% yield) as an off-white solid m.p. 86 - 87 ˚C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (d, 2H, J = 8.7 Hz), 7.82 (s, 1H), 7.46 (d, 2H, J = 8.5 Hz), 7.00 (d, 2H, J = 8.5 Hz), 6.81 (d, 2H, J = 8.6 Hz), 5.54 (s, 2H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 148.4, 135.9, 134.2, 133.6, 129.9, 128.6, 126.9, 124.2, 114.5, 55.4, 52.1; MS (EI): m/z: 310 (M^+); HRMS (ESI+): m/z calcd for $C_{16}H_{15}N_4O_3$ [M+H]+ : 311.1138, found 311.1130.

1-(4-Methoxybenzyl)-5-methyl-1H-1,2,3-triazole (132g): Acetone (72 mg, 1.26 mmol), 4- methoxybenzylamine (80 mg, 0.58 mmol), 4-nitrophenyl azide (68 mg, 0.42 mmol), acetic acid (8 mg, 0.13 mmol), 4 Å molecular sieves (50 mg) and toluene (0.4 mL). Reaction time is 12 h. The product was purified by flash column chromatography (DCM followed by heptane/EtOAc = 6:4) affording **132g** (52 mg, 62% yield) as an off-white solid. m.p. 69 - 70 ˚C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (s, 1H), 7.12 (d, 2H, J = 8.5 Hz), 6.87 (d, 2H, J = 8.5 Hz), 5.43 (s, 2H), 3.79

(s, 3H), 2.18 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.6, 133.6, 132.7, 128.8, 126.9, 114.4, 55.4, 51.3, 8.6; MS (EI): m/z: 203 (M^+); HRMS (ESI+): m/z calcd for $C_{11}H_{14}N_3O$ $[M+H]^+$: 204.1131, found 204.1131.

5-*tert*-Butyl-1-(4-methoxybenzyl)-1*H*-1,2,3-triazole (132h): Pinacolone (41 mg, 0.42 mmol), 4- methoxybenzylamine (80 mg, 0.58 mmol), 4-nitrophenyl azide (68 mg, 0.42 mmol), acetic acid (8 mg, 0.13 mmol), 4 Å molecular sieves (50 mg) and toluene (0.4 mL). The product was purified by flash column chromatography (DCM followed by heptane/EtOAc = 6:4) affording **132h** (85 mg, 83% yield) as an off white semi-solid. ^{1}H NMR (300 MHz, CDCl3) δ 7.46 (s, 2H), 7.02 (d, 2H, J = 8.8 Hz), 6.84 (d, 2H, J = 8.8Hz), 5.63 (s, 2H), 3.78 (s, 3H), 1.29 (s, 9H); ^{13}C NMR (75 MHz, CDCl3) δ 159.4, 145.5, 131.7, 128.2, 128.0, 114.3, 55.4, 52.6, 30.4, 30.0; MS (EI): m/z: 245 (M^+); HRMS (ESI+): m/z calcd for $C_{14}H_{20}N_3O$ $[M+H]^+$: 246.1601, found 246.1601.

5-(3,5-Bis(trifluoromethyl)phenyl)-1-(4-methoxybenzyl)-1*H*-1,2,3-triazole (132i): 3´,5´-Bis (trifluoromethyl)acetophenone (107 mg, 0.42 mmol), 4-methoxybenzylamine (80 mg, 0.58 mmol), 4- 12 nitrophenyl azide (68 mg, 0.42 mmol), (8 mg, 0.13 mmol), 4 Å molecular sieves (50 mg) and toluene (0.4 mL). Reaction time is 12 h. The product was purified by flash column chromatography (DCM followed by heptane/EtOAc = 6:4) affording **132i** (117 mg, 70% yield) as an off white solid. m.p. 70 - 71 ˚C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.82 (s, 1H), 7.63 (s, 2H), 7.02 (d, 2H, J = 8.5 Hz), 6.81 (d, 2H, J = 8.7 Hz), 5.50 (s, 2H), 3.78 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.0, 135.2, 134.3, 132.8, 132.3, 129.5, 129.3, 128.8, 126.6, 124.7, 123.3, 121.0, 114.6, 55.4, 52.4; MS (EI): m/z: 401 (M^+); HRMS (ESI+): m/z calcd for $C_{18}H_{14}F_6N_3O$ $[M+H]^+$: 402.1035, found 402.1039.

1-(4-Methoxybenzyl)-5-(1-naphthyl)-1*H*-1,2,3-triazole (132j): 1-Acetonaphthone (71 mg, 0.42 mmol), 4-methoxybenzylamine (80 mg, 0.58 mmol), 4-nitrophenyl azide (68 mg, 0.42 mmol), acetic acid (8 mg, 0.13 mmol), 4 Å molecular sieves (50 mg) and toluene (0.4 mL). Reaction time is 12 h. The product was purified by flash column chromatography (DCM followed by heptane/EtOAc = 6:4) affording

132j (105 mg, 80% yield) as an off white semi-solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 - 7.90 (m, 2H), 7.78 (s, 1H), 7.53 - 7.21 (m, 5H), 6.75 (d, 2H, J = 8.6 Hz), 6.61 (d, 2H, J = 8.6 Hz), 5.26 (s, 2H), 3.70 (s, 3H); ^{13}C NMR (75 MHz, CDCl3) δ 159.5, 135.8, 134.9, 133.6, 132.1, 130.4, 129.4, 129.0, 128.6, 127.3, 127.1, 126.6, 125.1, 124.9, 124.6, 113.9, 55.3, 51.9; MS (EI): m/z: 315 (M^+); HRMS (ESI+): m/z calcd for $C_{20}H_{18}N_3O$ $[M+H]^+$: 316.1444, found 316.1444.

1-(4-Methoxybenzyl)-5-(3-phenanthryl)-1*H*-1,2,3-triazole (132k): 3-Acetyl phenanthrene (92 mg, 0.42 mmol), 4-methoxybenzylamine (80 mg, 0.58 mmol), 4-nitrophenyl azide (68 mg, 0.42 mmol), acetic acid (8 mg, 0.13 mmol), 4 Å molecular sieves (50 mg) and toluene (0.4 mL). Reaction time is 12 h. The product was purified by flash column chromatography (DCM followed by heptane/EtOAc = 6:4) affording **132k** (138 mg, 91% yield) as an off white solid. m.p. 164 - 165 ˚C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (s, 1H), 8.24 (d, 1H, J = 7.2 Hz), 7.94 (t, 2H, J = 8.3 Hz), 7.88 (s, 1H), 7.84 - 7.75 (m, 2H), 7.66 - 7.58 (m, 2H), 7.50 (d, 1H, J = 8.3 Hz), 7.11 (d, 2H, J = 8.7 Hz), 6.85 (d, 2H, J = 8.7 Hz), 5.57 (s, 2H), 3.79 (s, 3H); ^{13}C NMR (75 MHz, CDCl3) δ 159.7, 138.5, 133.7, 132.4, 132.4, 130.3, 129.9, 129.4, 128.9, 128.8, 128.6, 128.1, 127.4, 127.1, 126.9, 126.4, 124.9, 123.8, 122.8, 114.5, 55.5, 51.8; MS (EI): m/z: 365 (M+); HRMS (ESI^+): m/z calcd for $C_{24}H_{20}N_{3O}$ $[M+H]^+$: 366.1601, found 366.1606.

2-(1-(4-Methoxybenzyl)-1*H*-1,2,3-triazol-5-yl)pyridine (132l): 2-Acetyl pyridine (51 mg, 0.42 mmol), 4- methoxybenzylamine (80 mg, 0.58 mmol), 4-nitrophenyl azide (68 mg, 0.42 mmol), 4 Å molecular sieves (50 mg) and toluene (0.4 mL). Reaction time is 24 h. The product was purified by flash column chromatography (DCM followed by heptane/EtOAc = 3:7) affording **132l** (91 mg, 82% yield) as an off white solid. m.p. 73 - 74 ˚C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.72 (d, 1H, J = 4.7 Hz), 7.98 (s, 1H), 7.77 - 7.71 (m, 1H), 7.55 - 7.52 (m, 1H), 7.31 - 7.27 (m, 1H), 7.20 (d, 2H, J = 8.3), 6.77 - 6.74 (m, 2H), 6.09 (s, 2H), 3.73 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 149.6, 147.2, 137.1, 135.5, 133.8, 129.5, 128.3, 123.4, 122.9, 113.9, 55.3, 52.6; MS (EI): m/z: 266 (M^+);

HRMS (ESI+): m/z calcd for $C_{15}H_{15}N_4O$ $[M+H]^+$: 267.1240, found 267.1241.

3-(1- (4-Methoxybenzyl)-1*H*-1,2,3-triazol-5-yl)-1H-indole (132m): 3-Acetyl indole (67mg, 0.42 mmol), 4- methoxybenzylamine (80 mg, 0.58 mmol), 4-nitrophenyl azide (68 mg, 0.42 mmol), acetic acid (8 mg, 0.13 mmol), 4 Å molecular sieves (50 mg) and toluene (0.4 mL). Reaction time is 12 h. The product was purified by flash column chromatography (DCM followed by heptane/EtOAc = 5:5) affording **132m** (106 mg, 83% yield) as an off white solid. m.p. 192 - 193 ˚C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.57 (sbr, 1H), 7.89 (s, 1H), 7.54 (d, 1H, J = 7.9 Hz), 7.46 (d, 1H, J = 8.1 Hz), 7.33 - 7.19 (m, 3H), 7.05 - 7.00 (m, 3H), 6.80 (d, 2H, J = 8.7 Hz), 5.53 (s, 2H), 3.77 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4, 136.0, 133.7, 132.6, 131.8, 128.5, 128.2, 126.3, 124.2, 123.4, 121.3, 119.3, 114.3, 111.7, 55.4, 51.4; MS (EI): m/z: 304 (M^+); HRMS (ESI+): m/z calcd for $C_{18}H_{17}N_4O$ $[M+H]^+$: 305.1397, found 305.1395.

5-(Furan-2-yl)-1- (4-methoxybenzyl)-1*H*-1,2,3-triazole (132n): 2-Acetyl furan (46 mg, 0.42 mmol), 4- methoxybenzylamine (80 mg, 0.58 mmol), 4-nitrophenyl azide (68 mg, 0.42 mmol), 4 Å molecular sieves (50 mg) and toluene (0.4 mL). Reaction time is 24 h. The product was purified by flash column chromatography (DCM followed by heptane/EtOAc = 6:4) affording **132n** (96 mg, 68% yield) as an off white semi-solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.55 - 7.54 (m, 1H), 7.13 (d, 2H, J = 88 Hz), 6.82 (d, 2H, J = 8.8 Hz), 6.53 - 6.48 (m, 2H), 5.71 (s, 2H), 3.77 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.6, 143.7, 141.5, 132.5, 128.9, 128.8, 127.3, 114.3, 111.9, 110.5, 55.4, 52.5; MS (EI): m/z: 255 (M^+); HRMS (ESI+): m/z calcd for $C_{14}H_{14}N_3O_2$ $[M+H]^+$: 256.1080, found 256.1082.

5-(1-(4-Methoxybenzyl)-1*H*-1,2,3-triazol-5-yl)pyrimidine-2,4 (1H,3H)-dione (132o): 5-Acetyluracil (64 mg, 0.42 mmol), 4-methoxybenzylamine (77 mg, 0.58 mmol), 4-nitrophenyl azide (68 mg, 0.42 mmol), 4 Å molecular sieves (50 mg) and DMF (0.6 mL). Reaction time is 12 h. The product was purified by flash column chromatography (DCM followed by DCM/MeOH = 95:5) affording **132o** (83 mg, 67%

yield) as an off-white solid. m.p. 253 - 254 ˚C. ^{1}H NMR (300 MHz, d_6-DMSO) δ 8.28 (s, 1H), 7.67 (s, 1H), 7.56 (s, 1H), 7.05 (d, 2H, J = 8.6 Hz), 6.85 (d, 2H, J = 8.6 Hz), 5.45 (s, 2H), 3.71 (s, 3H); ^{13}C NMR (75 MHz d6-DMSO) δ 162.3, 158.8, 151.7, 144.8, 137.5, 134.1, 129.7, 129.1, 127.8, 113.9, 55.1, 51.3; MS (EI): m/z: 299 (M^+); HRMS (ESI+): m/z calcd for $C_{14}H_{14}N_5O_3$ $[M+H]^+$: 300.1091, found 300.1096.

1-(4-Methoxybenzyl)-5-ferrocenyl-1*H*-1,2,3-triazole (132p): 1-Acetylferrocene (100 mg, 0.42 mmol), 4- methoxybenzylamine (168 mg, 1.2 mmol), 4-nitrophenyl azide (143 mg, 0.88 mmol), 4 Å molecular sieves (50 mg) and toluene (1 mL). Reaction time is 72 h. The product was purified by flash column chromatography (DCM followed by heptane/EtOAc = 2:8) affording **132p** (130 mg, 79% yield) as a red semisolid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.03 (d, 2H, J = 8.5 Hz), 6.86 (d, 2H, J = 8.5 Hz), 5.58 (s, 2H), 4.37 (s, 2H), 4.32 (s, 2H), 4.08 (s, 4H), 3.79 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 136.3, 133.1, 128.1, 127.9, 114.4, 70.9, 69.8, 69.6, 68.6, 55.4, 51.3; MS (EI): m/z: 373 (M^+); HRMS (ESI+): m/z calcd for $C_{20}H_{20}FeN_3O$ $[M+H]^+$: 374.0950, found 374.0958.

1-(4-Methoxybenzyl)-5-methyl-1*H*-1,2,3-triazole-4-carbaldehyde (132q): Propiophenone (56 mg,0.42 mmol), 4-methoxybenzylamine (80 mg, 0.58 mmol), 4-nitrophenyl azide (68 mg, 0.42 mmol), acetic acid (8 mg, 0.13 mmol), 4 Å molecular sieves (50 mg) and toluene (0.4 mL). Reaction time is 12 h. The product was purified by flash column chromatography (DCM followed by heptane/EtOAc = 6:4) affording **132q** (96 mg, 83% yield) as an off-white solid. m.p. 74 - 75 ˚C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 -7.42 (m, 3H), 7.17 - 7.13 (m, 2H), 6.99 - 6.94 (m, 2H), 6.79 - 6.74 (m, 2H), 5.35 (s, 2H), 3.76 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4, 141.7, 134.5, 129.7, 129.3, 129.0, 128.9, 127.8, 127.7, 114.1, 55.4, 51.7, 10.7; MS (EI): m/z: 279 (M^+); HRMS (ESI+): m/z calcd for $C_{17}H_{18}N_3O$ $[M+H]^+$: 280.1444, found 280.1443.

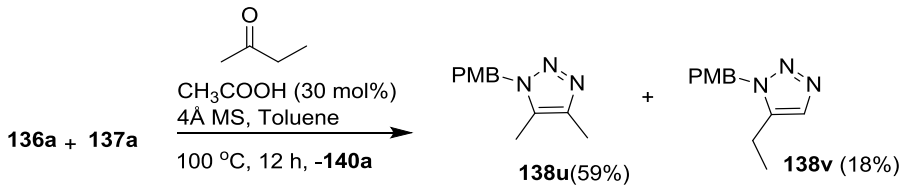
5-Butyl-1-(4-methoxybenzyl)-4-propyl-1*H*-1,2,3-triazole (132r): 5-nonanone (59 mg, 0.42 mmol), 4- methoxybenzylamine (80 mg, 0.58 mmol), 4-nitrophenyl azide (68 mg, 0.42 mmol), acetic acid (8 mg, 0.13

mmol), 4 Å molecular sieves (50 mg) and toluene (0.4 mL). Reaction time is 12 h. The product was purified by flash column chromatography (DCM followed by heptane/EtOAc = 6:4) affording **132r** (94 mg, 78% yield) as an off white semi-solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10 (d, 2H, J = 8.67 Hz), 6.85 (d, 2H, J = 8.67 Hz), 5.40 (s, 2H), 3.79 (s, 3H), 2.56 (t, 2H, J = 7.53 Hz), 2.46 (t, 2H, J = 7.71 Hz), 1.74 - 1.64 (m, 4H), 1.28 - 1.25 (m, 2H), 0.95 (t, 3H, J = 7.35 Hz), 0.87 - 0.82 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.6, 145.5, 133.2, 128.6, 127.7, 114.4, 55.4, 51.62, 31.0, 27.3, 23.0, 22.6, 22.4, 14.1, 13.8; MS (EI): m/z: 287 (M^+); HRMS (ESI+): m/z calcd for $C_{17}H_{26}N_3O$ $[M+H]^+$:288.2070, found 288.2072.

1-(4-Methoxybenzyl)-4-methyl-5-(thiophen-2-yl)-1*H*-1,2,3-triazole (132s): 2- Propanoyl thiophene (59 mg, 0.42 mmol), 4-methoxybenzylamine (80 mg, 0.58 mmol), 4-nitrophenyl azide (68 mg, 0.42 mmol), acetic acid (8 mg, 0.13 mmol), 4 Å molecular sieves (50 mg) and toluene (0.4 mL). Reaction time is 12 h. The product was purified by flash column chromatography (DCM followed by heptane/EtOAc =6:4) affording **132s** (106 mg, 89% yield) as an off white semi-solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 - 7.47 (m, 1H), 7.13 - 7.10 (m, 1H), 7.01 (d, 2H, J = 8.5 Hz), 6.95 - 6.94 (m, 1H), 6.80 (d, 2H, J = 8.7 Hz), 5.46 (s, 2H), 3.76 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 142.9, 129.3, 128.7, 128.3, 128.1, 127.7, 127.6, 127.0, 114.1, 55.3, 51.8, 11.0; MS (EI): m/z: 285 (M^+); HRMS (ESI+): m/z calcd for $C_{15}H_{16}N_3OS$ $[M+H]^+$: 286.1008, found 286.1009.

2-(5- (9-Ethyl-9H-carbazol-3-yl)-1-(4-methoxybenzyl)-1*H*-1,2,3-triazol-4-yl)acetic acid (132t): 4-(9-Ethyl-9*H*-carbazol-3-yl)-4-oxobutanoic acid (50 mg, 0.17 mmol), 4-methoxybenzylamine (49 mg, 0.35 mmol), 4-nitrophenyl azide (30 mg, 0.0.17 mmol), acetic acid (3 mg, 0.05 mmol), 4 Å molecular sieves (10 mg) and toluene (0.4 mL). Reaction time is 40 h. The product was purified by flash column chromatography (DCM followed by heptane/EtOAc = 1:9) affording **132t** (53 mg, 74 %) as an off white solid. m.p. 90 - 91 ˚C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, 1H, J = 7.9Hz), 7.80 (s, 1H), 7.52 - 7.44 (m, 3H), 7.28 - 7.23 (m, 2H), 7.03 (d, 2H, J = 8.6 Hz), 6.79 (d, 2H, J = 8.5 Hz), 5.40 (s, 2H), 4.41 (q, 2H, J = 7.2 Hz), 3.78 – 3.76 (m, 5H), 17 1.47 (t, 3H, J =

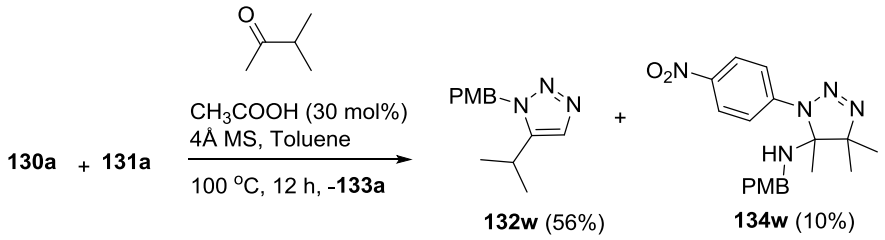
7.1Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 159.6, 140.5, 138.6, 137.2, 129.3, 127.7, 127.1, 126.7, 123.3, 122.5, 122.3, 120.8, 119.7, 115.9, 114.3, 109.1, 109.0, 55.4, 52.0, 37.2, 29.8, 14.0; MS (EI): m/z: 440 (M^+); HRMS (ESI+): m/z calcd for $C_{26}H_{25}N_4O_3$ $[M+H]^+$: 441.1921, found 441.1924.



2-Butanone (30mg, 0.44 mmol), 4-methoxybenzylamine (80 mg, 0.58 mmol), 4-nitrophenyl azide (68 mg, 0.42 mmol), acetic acid (8 mg, 0.13 mmol), 4 Å molecular sieves (50 mg) and toluene (0.4 mL). Reaction time is 12 h. The products was purified by flash column chromatography (DCM followed by heptane/EtOAc =7:3) affording **132u** (53 mg, 59% yield) and **132v** (16 mg, 18% yield) as colorless semi-solids.

1-(4-Methoxybenzyl)-4,5-dimethyl-1*H*-1,2,3-triazole (132u): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.11 (d, 2H, *J* = 8.5 Hz), 6.85 (d, 2H, *J* = 8.5 Hz), 5.38 (s, 2H), 3.78 (s, 3H), 2.24 (s, 3H), 2.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 141.2, 129.1, 128.7, 127.1, 114.3, 55.4, 51.6, 10.3, 8.0; MS (EI): m/z: 217 (M^+); HRMS (ESI^+): m/z calcd for $C_{12}H_{16}N_3O$ $[M+H]^+$: 218.1289, found 218.1284.

5-Ethyl-1- (4-methoxybenzyl)-1*H*-1,2,3-triazole (132v): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (s, 1H), 7.11 (d, 2H, *J* = 8.6 Hz), 6.85 (d, 2H, *J* = 8.6 Hz), 5.43 (s, 2H), 3.79 (s, 3H), 2.51 (q, 2H, *J* = 7.7 Hz), 1.19 (t, 3H, *J* = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.6, 138.7, 132.2, 128.7, 127.0, 114.4, 55.4, 51.3, 16.9, 12.2; MS (EI): m/z: 217 (M^+); HRMS (ESI^+): m/z calcd for $C_{12}H_{16}N_3O$ $[M+H]^+$: 218.1289, found 218.1282.



Methyl isopropyl ketone (36 mg, 0.42 mmol), 4-methoxybenzylamine (80 mg, 0.58 mmol), 4- nitrophenyl azide (68 mg, 0.42 mmol), acetic acid (8 mg, 0.13 mmol), 4 Å molecular sieves (50 mg) and toluene (0.4 mL). Reaction time is 12 h. The products was purified by flash column chromatography (DCM followed by heptane/EtOAc = 5:5) affording **132w** (54 mg, 56% yield) and **141w** (15 mg, 10% yield) as a colorless semi-solid.

5-Isopropyl-1-(4-methoxybenzyl)-1*H*-1,2,3-triazole (132w): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (s, 1H), 7.11 (d, 2H, J = 8.8 Hz), 6.85 (d, 2H, J = 8.6Hz), 5.46 (s, 2H), 3.79 (s, 3H), 2.92 - 2.83 (m, 1H), 1.15 (d, 6H, J = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.6, 143.5, 130.9, 128.6, 127.3, 114.4, 55.4, 51.3, 23.9, 22.5; MS (EI): m/z: 231 (M^+); HRMS (ESI+): m/z calcd for $C_{13}H_{17}N_3O$ $[M+H]^+$: 232.1444, found 232.1449.

***N*-(4-Methoxybenzyl)-4,4,5-trimethyl-1-(4-nitrophenyl)-4,5-dihydro-1*H*-1,2,3-triazol-5-amine (134w):** ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, 2H, J = 8.8 Hz), 7.07 (d, 2H, J = 8.2 Hz), 6.84 (d, 2H, J = 8.5 Hz), 6.75 (d, 2H, J = 8.7 Hz), 4.86 (s, 1H), 3.94 (s, 2H), 3.80 (s, 3H), 1.24 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.8, 18 159.3, 141.0, 130.2, 129.0, 124.9, 120.7, 114.3, 71.8, 70.5, 55.4, 48.0, 39.2, 29.7, 29.3; MS (EI): m/z: 369 (M+); HRMS (ESI+): m/z calcd for $C_{19}H_{24}N_5O_3$ $[M+H]^+$: 370.1873, found 370.1877.

1-(4-Methoxybenzyl)-4,5,6,7-tetrahydro-1*H*-benzo[d][1,2,3]triazole (132x): Cyclohexanone (41 mg, 0.84 mmol), 4-methoxybenzylamine (80 mg, 0.58 mmol), 4-nitrophenyl azide (68 mg, 0.42 mmol), acetic acid (8 mg, 0.13 mmol), 4 Å molecular sieves (50 mg) and toluene (0.4 mL). Reaction time is 12 h. The product was purified by flash column

chromatography (DCM followed by heptane/EtOAc = 6:4) affording **132x** (91 mg, 91% yield) as a solid. m.p. 91 - 92 ˚C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15 (d, 2H, J = 8.8 Hz), 6.85 (d, 2H, J = 8.8Hz), 5.36 (s, 2H), 3.79 (s, 3H), 2.74 - 2.72 (m, 2H), 2.43 - 2.39 (m, 2H), 1.78 - 1.73 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.6, 144.0, 131.9, 129.1, 127.1, 114.3, 55.4, 51.5, 22.6, 22.5, 22.0, 20.2; MS (EI): m/z: 243 (M+); HRMS (ESI+): m/z calcd for $C_{14}H_{18}N_3O$ $[M+H]^+$: 244.1444, found 244.1440.

1-(4-Methoxybenzyl)-4,5,6,7,8,9-hexahydro-1*H*-cycloocta[d][1,2,3]triazole (132y): Cyclooctanone (52 mg, 0.42mmol), 4-methoxybenzylamine (77 mg, 0.58 mmol), 4-nitrophenyl azide (68 mg, 0.42 mmol), acetic acid (8 mg, 0.13 mmol), 4 Å molecular sieves (50 mg) and toluene (0.4 mL). Reaction time is 12 h. The product was purified by flash column chromatography (DCM followed by heptane/EtOAc = 6:4) affording **132y** (101 mg, 89% yield) as a semi-solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10 (d, 2H, J = 8.8 Hz), 6.84 (d, 2H, J = 8.7 Hz), 5.39 (s, 2H), 3.78 (s, 3H), 2.89 (t, 2H, J = 6.4 Hz), 2.62 (t, 2H, J = 6.2 Hz), 1.74 - 1.72 (m, 2H), 1.54 - 1.50 (m, 2H), 1.39 - 1.37 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 145.3, 133.2, 128.6, 127.6, 114.3, 55.4, 51.4, 28.4, 26.0, 26.0, 24.9, 24.7, 21.9; MS (EI): m/z: 271 (M^+); HRMS (ESI+): m/z calcd for $C_{16}H_{22}N_3O$ [M+H]+ : 272.1757, found 272.1755.

1-(4-Methoxybenzyl)-4,5,6,7,8,9, 10, 11, 12, 13-decahydro-1*H*-cyclododeca[d][1,2,3]triazole (132z): Cyclododecanone (76 mg, 0.42 mmol), 4-methoxybenzylamine (80 mg, 0.58 mmol), 4-nitrophenyl 19 azide (68 mg, 0.42 mmol), acetic acid (8 mg, 0.13 mmol), 4 Å molecular sieves (50 mg) and toluene (0.4 mL). Reaction time is 12 h. The product was purified by flash column chromatography (DCM followed by heptane/EtOAc = 6:4) affording **132z** (132 mg, 95% yield as a semisolid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09 (d, 2H, J = 8.7 Hz), 6.84 (d, 2H, J = 8.7 Hz), 5.42 (s, 2H), 3.78 (s, 3H), 2.59 (t, 2H, J = 7.0 Hz), 2.49 (t, 2H, J = 7.2 Hz), 1.88 - 1.80 (m, 2H), 1.61 - 1.52 (m, 2H), 1.42 - 1.19 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 146.1, 133.3, 128.5, 127.5, 114.3, 55.4, 51.7, 27.7, 26.2, 25.3, 24.8, 24.8, 24.5, 22.6, 22.6, 22.0, 19.6; MS (EI):

m/z: 327 (M^+); HRMS (ESI+): m/z calcd for $C_{20}H_{30}N_3O$ $[M+H]^+$: 328.2383, found 328.2382.

1-(4-Methoxybenzyl)-1,4,6,7-tetrahydropyrano[3,4-d][1,2,3]triazole (132aa): Tetrahydro-4*H*-pyran-4- one (42 mg, 0.42 mmol), 4-methoxybenzylamine (80 mg, 0.58 mmol), 4-nitrophenyl azide (68 mg, 0.42 mmol), 4 Å molecular sieves (50 mg) and toluene (0.4 mL). Reaction time is 24 h. The product was purified by flash column chromatography (DCM followed by heptane/EtOAc = 6:4) affording **132aa** (78 mg, 76% yield) as an off white solid. m.p. 75 - 76 ˚C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (d, 2H, J = 8.8 Hz), 6.87 (d, 2H, J = 8.8 Hz), 5.42 (s, 2H), 4.80 (s, 2H), 3.85 (t, 2H, J = 5.5), 3.80 (s, 3H), 2.55 (t, 2H, J = 5.5); ^{13}C NMR (75 MHz, CDCl3) δ 159.9, 142.3, 129.5, 129.3, 126.5, 114.5, 64.2, 64.0, 55.4, 51.9, 22.0; MS (EI): m/z: 245 (M^+); HRMS (ESI+): m/z calcd for $C_{13}H_{16}N_3O_2$ $[M+H]^+$: 246.1237, found 246.1239.

5-Benzyl-1-(4-methoxybenzyl)-4,5,6,7-tetrahydro-1*H*-[1,2,3]triazolo[4,5-c]pyridine (132ab): 1- Benzylpiperidin-4-one (79 mg, 0.42 mmol), 4-methoxybenzylamine (80 mg, 0.58 mmol), 4-nitrophenyl azide (68 mg, 0.42 mmol), 4 Å molecular sieves (50 mg) and toluene (0.4 mL). Reaction time is 24 h. The product was purified by flash column chromatography (DCM followed by heptane/EtOAc = 5:2) affording **132ab** (107 mg, 78% yield) as an off-white solid. m.p. 75 -76 ˚C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 - 7.26 (m, 5H), 7.16 (d, 2H, J = 8.7 Hz), 6.85 (d, 2H, J = 8.6 Hz), 5.36 (s, 2H), 3.78 (s, 3H), 3.70 (s, 2H), 3.67 (s, 2H), 2.71 (t, 2H, J = 5.8 Hz), 2.49 (t, 2H, J = 5.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.7, 142.9, 138.0, 130.5, 129.3, 129.1, 128.5, 127.4, 126.7, 114.4, 61.9, 55.4, 51.8, 49.9, 49.3, 21.0; MS (EI): m/z: 334 (M^+); HRMS (ESI+): m/z calcd for $C_{20}H_{23}N_4O$ $[M+H]^+$: 335.1866, found 335.1869.

3-(4-Methoxybenzyl)-3,8-dihydroindeno[1,2-d][1,2,3]triazole (132ac): 1-indanone (55 mg, 0.42 mmol), 4-methoxybenzylamine (80 mg, 0.58 mmol), 4-nitrophenyl azide (68 mg, 0.42 mmol), acetic acid (8 mg, 0.13 mmol), 4 Å molecular sieves (50 mg) and toluene (0.4 mL). Reaction time is 12 h. The product was purified by flash column

chromatography (DCM followed by heptane/EtOAc = 6:4) affording **132ac** (99 mg, 95% yield) as an off white solid. m.p. 110 - 111 ˚C. 1H NMR (300 MHz, CDCl3) δ 7.52 - 7.49 (m, 1H), 7.29 - 7.25 (m, 4H), 7.13 (t, 1H, J = 8.6 Hz), 6.88 (d, 2H, J = 8.6 Hz), 5.70 (s, 2H), 3.78 (s, 3H), 3.79 (s, 2H); 13C NMR (75 MHz, CDCl3) δ 159.8, 155.9, 147.6, 141.3, 129.8, 129.0, 127.3, 127.2, 127.0, 126.7, 120.1, 114.6, 55.4, 53.1, 29.1; MS (EI): m/z: 277 (M+); HRMS (ESI+): m/z calcd for $C_{17}H_{16}N_3O$ $[M+H]^+$: 278.1288, found 278.1281.

1-(4-Methoxybenzyl)-4,5-dihydro-1*H*-naphtho[1,2-d][1,2,3]triazole (132ad): 1-Tetralone (61 mg, 0.42mmol), 4-methoxybenzylamine (80 mg, 0.58 mmol), 4-nitrophenyl azide (68 mg, 0.42 mmol), acetic acid (8 mg, 0.13 mmol), 4 Å molecular sieves (50 mg) and toluene (0.4 mL). Reaction time is 12 h. The product was purified by flash column chromatography (DCM followed by heptane/EtOAc = 6:4) affording **132ad** (103 mg, 85% yield) as a solid. m.p. 84 ˚C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 - 7.30 (m, 2H), 7.28 - 7.17 (m, 2H), 7.12 (d, 2H, J = 8.8 Hz), 6.85 (d, 2H, J = 8.8Hz), 5.77 (s, 2H), 3.76 (s, 3H), 3.02 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 145.7, 137.3, 131.4, 129.2, 128.5, 127.9, 127.3, 127.2, 125.0, 122.7, 114.5, 55.3, 52.7, 30.3, 20.8; MS (EI): m/z: 291 (M^+); HRMS (ESI+): m/z calcd for $C_{18}H_{18}N_3O$ $[M+H]^+$: 292.1444, found 292.1447.

1-(4-Methoxybenzyl)-1,4,5,6-tetrahydrobenzo[3,4]cyclohepta[1,2-d][1,2,3]triazole (132ae): 1- Benzosuberone (67 mg, 0.42 mmol), 4-methoxybenzylamine (80 mg, 0.58 mmol), 4-nitrophenyl azide (68 mg, 0.42 mmol), acetic acid (8 mg, 0.13 mmol), 4 Å molecular sieves (50 mg) and toluene (0.4 mL). Reaction time is 12 h. The product was purified by flash column chromatography (DCM followed by heptane/EtOAc = 6:4) affording **132ae** (119 mg, 94% yield) as an off white semi-solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 - 7.24 (m, 4H), 7.16 (d, 2H, J = 8.7 Hz), 6.83 (d, 2H, J = 8.7 Hz), 5.59 (s, 2H), 3.77 (s, 3H), 2.93 (t, 2H, J = 7.3 Hz), 2.57 (t, 2H, J = 6.0 Hz), 2.23 - 2.14 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4, 146.1, 142.4, 133.1, 130.1, 128.9, 128.3, 127.5, 126.8, 126.6, 114.3, 55.3, 51.7, 32.8, 29.9, 23.3; MS (EI): m/z:

305 (M^+); HRMS (ESI+): m/z calcd for $C_{19}H_{20}N_3O$ $[M+H]^+$: 306.1601, found 306.1605.

1-(4-Methoxybenzyl)-1,8-dihydroindeno[1,2-d][1,2,3]triazole (132af): 2-Indanone (55 mg, 0.42mmol), 4-methoxybenzylamine (80 mg, 0.58 mmol), 4-nitrophenyl azide (68 mg, 0.42 mmol), acetic acid (8 mg, 0.13 mmol), 4 Å molecular sieves (50 mg) and toluene (0.4 mL). Reaction time is 12 h. The product was purified by flash column chromatography (DCM followed by heptane/EtOAc = 6:4) affording **132af** (86 mg, 75% yield) as an off white semi-solid. ^{1}H NMR (300 MHz, CDCl3) δ 7.79 - 7.76 (m, 1H), 7.34 - 7.27 (m, 4H), 7.21 - 7.16 (m, 1H), 6.91 (d, 2H, J = 8.7 Hz), 5.54 (s, 2H), 3.81 (s, 3H), 3.24 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.1, 156.4, 144.8, 141.9, 133.7, 130.2, 127.6, 126.1, 125.9, 125.8, 119.9, 114.6, 55.5, 53.3, 28.0; MS (EI): m/z: 277 (M^+); HRMS (ESI+): m/z calcd for $C_{17}H_{16}N_3O$ $[M+H]^+$: 278.1288, found 278.1288.

3-(4-Methoxybenzyl)-4,5-dihydro-3*H*-naphtho[1,2-d][1,2,3]triazole (132ag): 2-Tetralone (61 mg, 0.42 mmol), 4-methoxybenzylamine (80 mg, 0.58 mmol), 4-nitrophenyl azide (68 mg, 0.42 mmol), acetic acid (8 mg, 0.13 mmol), 4 Å molecular sieves (50 mg) and toluene (0.4 mL). Reaction time is 12 h. The product was purified by flash column chromatography (DCM followed by heptane/EtOAc = 6:4) affording **132ag** (100 mg, 82% yield) as a semi solid. ^{1}H NMR (300 MHz, CDCl3) δ 7.93 (d, 1H, J = 7.3 Hz), 7.30 - 7.26 (m, 1H), 7.18 - 7.15 (m, 4H), 6.85 (d, 2H, J = 8.6 Hz), 5.47 (s, 2H), 3.78 (s, 3H), 3.0 (t, 2H, J = 7.7 Hz), 2.72 (t, 2H, J = 7.8 Hz); ^{13}C NMR (75 MHz, CDCl3) δ 159.7, 144.1, 133.4, 132.6, 129.0, 128.7, 128.2, 127.5,127.4, 126.9, 122.1, 114.5, 55.4, 51.8, 28.5, 19.1; MS (EI): m/z: 291 (M^+); HRMS (ESI+): m/z calcd for $C_{18}H_{18}N_3O$ $[M+H]^+$: 292.1443, found 292.1445

2-((5-Phenyl-1*H*-1,2,3-triazol-1-yl)methyl)pyridine (132ah): Acetophenone (52 mg, 0.42 mmol), pyridin- 2-ylmethanamine (64 mg, 0.59 mmol), 4-nitrophenyl azide (68 mg, 0.42 mmol), 4 Å molecular sieves (50 mg) and toluene (0.4 mL). Reaction time is 24 h. The product was purified by flash column chromatography (DCM followed by

heptane/EtOAc =2:8) affording **132ah** (70 mg, 67% yield) as an off white semi-solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.56 (d, 1H, J = 5), 7.80 (s, 1H), 7.67 – 7.62 (m, 1H), 7.42 -7.40 (m, 5H), 7.27 -7.20 (m, 1H), 7.03 (d, 1H, J = 8), 5.70 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.5, 149.7, 138.8, 137.2, 133.2, 129.6, 129.1, 128.9, 126.7, 123.1, 121.7, 53.4; MS (EI): m/z: 236 (M^+); HRMS (ESI+): m/z calcd for $C_{14}H_{12}N_4$ [M+H]+ : 265.1448, found 265.1442.

3-(1-(3,4,5-Trimethoxybenzyl)-*1H*-1,2,3-triazol-5-yl)-1*H*-indole (132ai): 3-Acetylindole (66 mg, 0.42 mmol), 3,4,5-trimethoxybenzylamine (115 mg, 0.58 mmol), 4-nitrophenyl azide (68 mg, 0.42 mmol), acetic acid (8 mg, 0.13 mmol), 4 Å molecular sieves (50 mg) and toluene (0.4 mL). Reaction time is 12 h. The product was purified by flash column chromatography (DCM followed by heptane/EtOAc = 6:4) affording **132ai** (119 mg, 78% yield) as an off-white solid. m.p. 180 - 181 ˚C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.31 (s, 1H), 7.89 (s, 1H), 7.50 - 7.46 (m, 2H), 7.31 - 7.26 (m, 1H), 7.22 - 7.16 (m, 1H), 7.13 (d, 1H, J = 2.6 Hz), 6.23 (s, 2H), 5.52 (s, 2H),3.79 (s, 3H), 3.63 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.5, 137.6, 136.1, 133.7, 132.2, 131.6, 126.3, 124.5, 123.3, 121.2, 119.2, 111.9, 104.3, 102.1, 60.9, 56.0, 52.1; MS (EI): m/z: 364 (M^+); HRMS (ESI+): m/z calcd for $C_{20}H_{21}N_4O_3$ $[M+H]^+$: 365.1608, found 365.1610.

1-(4-Fluorobenzyl)-4,5-dihydro-1*H*-naphtho[1,2-d][1,2,3]triazole (132aj): 1-Tetralone (61 mg, 0.42 mmol), 4-flurobenzylamine (73 mg, 0.58 mmol), 4-nitrophenyl azide (68 mg, 0.42 mmol), acetic acid (8 23 mg, 0.13 mmol), 4 Å molecular sieves (50 mg) and toluene (0.4 mL). Reaction time is 12 h. The product was purified by flash column chromatography (DCM followed by heptane/EtOAc = 5:2) affording **132aj** (92 mg, 79% yield) as an off white semi-solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 - 7.14 (m, 6H), 7.06 - 7.0 (m, 2H), 5.81 (s, 2H), 3.04 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.2, 161.0, 145.9, 137.4, 131.5, 131.1, 131.0, 129.4, 128.7, 128.5, 128.4, 127.2, 124.9, 122.5, 116.4, 116.1, 52.5, 30.4, 20.8; MS (EI): m/z: 279 (M^+); HRMS (ESI+): m/z calcd for $C_{17}H_{15}FN_3$ $[M+H]^+$: 280.1244, found 280.1242.

***N*-(2-(5-Phenyl-1*H*-1,2,3-triazol-1-yl)ethyl)aniline (132ak):** Acetophenone (52 mg, 0.42 mmol), phenylmethanediamine (71 mg, 0.59 mmol), 4-nitrophenyl azide (68 mg, 0.42 mmol), 4 Å molecular sieves (50 mg) and toluene (0.4 mL). Reaction time is 24 h. The product was purified by flash column chromatography (DCM followed by DCM/MeOH = 95:5) affording **132ak** (69 mg, 62% yield) as an off white semi solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.48 - 7.45 (m, 3H), 7.41 - 7.35 (m, 2H), 7.30 - 7.21 (m, 5H), 4.45 (t, 2H, J = 6 Hz), 3.10 (t, 2H, J = 6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.7, 138.3, 133.1, 129.6, 129.2, 129.0, 128.5, 128.1, 127.2, 127.1, 53.3, 48.2; MS (EI): m/z: 264 (M^+); HRMS (ESI+): m/z calcd for $C_{16}H_{17}N_4$ $[M+H]^+$: 265.1448, found 265.1442.

4-(5-Phenyl-1*H*-1,2,3-triazol-1-yl)piperidine (132al): Acetophenone (50 mg, 0.42 mmol), 4- piperidineamine (58 mg, 0.58 mmol), 4-nitrophenyl azide (68 mg, 0.42mmol), 4 Å molecular sieves (50 mg) and toluene (0.4 mL). Reaction time is 24 h. The product was purified by flash column chromatography (DCM followed by DCM/MeOH = 95:5) affording **132al** (53 mg, 56% yield) as an off white semi-solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (s, 1H), 7.53 - 7.50 (m, 3H), 7.36 - 7.33 (m, 2H), 4.39 - 4.32 (m, 1H), 3.29 - 3.24 (m, 2H), 2.72 - 2.64 (m, 2H), 2.36 - 2.30 (m, 2H), 2.28 - 1.98 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.2, 133.0, 129.6, 129.3, 129.1, 127.5, 56.5, 45.8, 34.1; MS (EI): m/z: 228 (M^+); HRMS (ESI+): m/z calcd for $C_{13}H_{17}N_4$ $[M+H]^+$: 229.1448, found 229.1445.

1-Allyl-5-phenyl-1*H*-1,2,3-triazole (132am): Acetophenone (52 mg, 0.42 mmol), allylamine (34 mg, 0.59 mmol), 4-nitrophenyl azide (68 mg, 0.42 mmol), 4 Å molecular sieves (50 mg) and toluene (0.4 mL). Reaction time is 24 h. The product was purified by flash column chromatography (DCM followed by heptane/EtOAc = 6:4) affording **132am** (49 mg, 61% yield) as an off white semi-solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.50 - 7.40 (m, 5H), 6.09 - 5.96 (m, 1H), 5.27 (d, 1H, J = 9.3 Hz), 5.07 - 4.97 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.1, 133.1, 132.2, 129.6, 129.1, 128.8, 127.0, 118.8, 50.6; MS (EI): m/z: 185

(M^+); HRMS (ESI+): m/z calcd for $C_{11}H_{12}N_3$ $[M+H]^+$: 186.1026, found 186.1028.

1-(2,2-Dimethoxyethyl)-5-phenyl-1*H*-1,2,3-triazole (132an): Acetophenone (50 mg, 0.42 mmol), 2,2- dimethoxyethanamine (61 mg, 0.58 mmol), 4-nitrophenyl azide (68 mg, 0.42 mmol), 4 Å molecular sieves (50 mg) and toluene (0.4 mL). Reaction time is 24 h. The product was purified by flash column chromatography (DCM followed by heptane/EtOAc = 6:4) affording **132an** (79 mg, 82% yield) as an offwhite solid. m.p. 120 - 121 ˚C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.49 - 7.48 (m, 5H), 4.89 (t, 1H, J = 7.6 Hz), 4.41 (d, 2H, J = 7.5 Hz), 3.33 (s, 6H); ^{13}C NMR (100 MHz, CDCl3) δ 138.9, 132.8, 129.5, 129.2, 129.0, 126.9, 103.4, 55.2, 49.6; MS (EI): m/z: 233 (M^+); HRMS (ESI+): m/z calcd for $C_{12}H_{16}N_3O_2$ $[M+H]^+$: 234.1237, found 234.1238.

(S)-5-Phenyl-1- (1-phenylethyl)-1*H*-1,2,3-triazole (132ao): Acetophenone (50 mg, 0.42 mmol), (S)-(−)-α- methylbenzylamine (71 mg, 0.58 mmol), 4-nitrophenyl azide (68 mg, 0.42 mmol), acetic acid (8 mg, 0.13 mmol), 4 Å molecular sieves (50 mg) and toluene (0.4 mL). Reaction time is 48 h. The product was purified by flash column chromatography (DCM followed by heptane/EtOAc = 5:2) affording **132ao** (91 mg, 87% yield) as an off-white solid. m.p. 53 - 54 ˚C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.42 - 7.40 (m, 3H), 7.31 - 7.26 (m, 3H), 7.20 - 7.17 (m, 4H), 5.57 (q, 1H, J = 7.1 Hz), 2.02 (d, 3H, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.4, 138.0, 133.3, 129.5, 129.4, 129.0, 128.9, 128.1, 127.3, 126.3, 58.5, 22.9; MS (EI): m/z: 249 (M^+); HRMS (ESI+): m/z calcd for $C_{16}H_{16}N_3$ [M+H]+ : 250.1339, found 250.1339.

(S)-2-(5-Phenyl-1*H*-1,2,3-triazol-1-yl)butan-1-ol (132ap): Acetophenone (50 mg, 0.42 mmol), (S)-2- aminobutan-1-ol (51 mg, 0.58 mmol), 4-nitrophenyl azide (68 mg, 0.42 mmol), 4 Å molecular sieves (50 mg) and toluene (0.4 mL). Reaction time is 48 h. The product was purified by flash column chromatography (DCM followed by heptane/EtOAc = 4:6) affording **132ap** (75 mg, 83% yield) as an off white semi-solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (s, 1H), 7.50 - 7.44 (m, 5H), 4.46 - 4.31 (m, 2H), 4.0 - 3.97 (m, 1H), 3.73 (sbr, 1H), 2.06 -

1.79 (m, 2H), 0.69 (t, 3H, J = 7.3Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.6, 132.4, 129.6, 129.6, 129.1, 127.1, 65.0, 62.1, 25.1, 10.4; MS (EI): m/z: 217 (M+); HRMS (ESI+): m/z calcd for $C_{12}H_{16}N_3O$ $[M+H]^+$: 218.1288, found 218.1287.

1-(4-Methoxyphenyl)-5-phenyl-1*H*-1,2,3-triazole (132aq): Acetophenone (50 mg, 0.42 mmol), 4- methoxyaniline (72 mg, 0.58 mmol), 4-nitrophenyl azide (68 mg, 0.42 mmol), acetic acid (8 mg, 0.13 mmol), 4 Å molecular sieves (50 mg) and toluene (0.4 mL). Reaction time is 48 h. The product was purified by flash column chromatography (DCM followed by heptane/EtOAc = 6:4) affording **132aq** (26 mg, 25% yield) as an off-white solid. m.p. 160 - 161 ˚C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.36 - 7.24 (m, 7H), 6.93 (d, 2H, J = 8.8 Hz), 3.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.2, 137.4, 133.3, 129.7, 129.3, 129.0, 128.7, 127.0, 126.7, 114.6, 55.7; MS (EI): m/z: 251 (M^+); HRMS (ESI+): m/z calcd or $C_{15}H_{14}N_3O$ $[M+H]^+$: 252.1131, found 252.1132.

1,1'-Bis(1-(4-methoxybenzyl)-1*H*-1,2,3-triazol-5-yl)ferrocene (139): 1, 1'-Diacetylferrocene (100 mg, 0.37 mmol), 4-methoxybenzylamine (282 mg, 2.07 mmol), 4-nitrophenyl azide (121 mg, 0.74 mmol), 4 Å molecular sieves (50 mg) and toluene (1 mL). Reaction time is 72 h. The product was purified by flash column chromatography (DCM followed by heptane/EtOAc = 2:8) affording **139** (140 mg, 68% yield) as a red solid. m.p. 100 - 101 ˚C. ^{1}H NMR (300 MHz, CDCl3) δ 7.65 (s, 2H), 6.96 (d, 4H, J = 8.4 Hz), 6.84 (d, 4H, J = 8.5 Hz), 5.42 (s, 4H), 4.26 (s, 4H), 4.18 (s, 4H), 3.79 (s, 6H); ^{13}C NMR (75 MHz, CDCl3) δ 159.6, 135.1, 133.3, 128.1, 127.5, 114.5, 72.2, 71.7, 70.0, 55.5, 51.5; MS (EI): m/z: 560 (M+); HRMS (ESI+): m/z calcd for $C_{30}H_{29}FeN_6O_2$ $[M+H]^+$: 561.1695, found 561.1691.

1,3,5-Tris (1- (4-methoxybenzyl)-1H-1,2,3-triazol-5-yl)benzene (140): 1,3,5-Triacetylbenzene (50 mg, 0.24 mmol), 4-methoxybenzylamine (140 mg, 1.03 mmol), 4-nitrophenyl azide (144 mg, 0.88 mmol), acetic acid (4 mg, 0.06 mmol), 4 Å molecular sieves (50 mg) and toluene (0.8 mL). Reaction time is 48 h. The product was purified by flash column chromatography (DCM followed by heptane/EtOAc = 2:8) affording

140 (118 mg, 77% yield) an off-white solid. m.p. 167 - 168 ˚C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (s, 3H), 7.28 (s, 3H), 6.84 (d, 6H, J = 8.6 Hz), 6.73 (d, 6H, J = 8.8Hz), 5.35 (s, 6H), 3.72 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.8, 135.7, 133.9, 129.7, 128.8, 128.5, 126.9, 114.4, 55.4, 52.0; MS (EI): m/z: 639 (M^+); HRMS (ESI+): m/z calcd for $C_{36}H_{34}N_9O_3$ $[M+H]^+$: 640.2779, found 640.2781.

Tris (2-(5-phenyl-1H-1,2,3-triazol-1-yl)ethyl)amine (141): Acetophenone (295 mg, 2.4 mmol), tris(2- aminoethyl)amine (100 mg, 0.68 mmol), 4-nitrophenyl azide (370 mg, 2.2 mmol), acetic acid (4 mg, 0.06 mmol) 4 Å molecular sieves (30 mg) and toluene (0.6 mL).Reaction time is 48 h. The product was purified by flash column chromatography (DCM followed by DCM/MeOH= 95:5) affording **141** (230 mg, 65% yield) an off-white solid. m.p. 167 - 168 ˚C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (s, 3H), 7.48 - 7.46 (m, 9H), 7.29 - 7.27 (m, 6H), 4.08 - 4.03 (t, 6H, J = 6.6), 2.74 - 2.70 (t, 6H, J = 6.96); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.1, 133.2, 129.8, 129.4, 128.8, 127.0, 53.5, 46.2; MS (EI): m/z: 530 (M^+); HRMS (ESI+): m/z calcd for $C_{30}H_{31}N_{10}$ $[M+H]^+$: 531.2727, found 531.2728.

1,*N*1'-(Butane-1,4-diyl)bis(*N*1-(3-(bis(3-(4,5,6,7-tetrahydro-1H-benzo[d][1,2,3]triazol-1- yl)propyl)amino)propyl)-N3,N3-bis(3-(4,5,6,7-tetrahydro-1*H*-benzo[d][1,2,3]triazol-1- yl)propyl)propane-1,3-diamine) (143): Poly(propylene imine)-dendrimer of generation 2 (70 mg, 0.09 mmol), cyclohexanone (106 mg, 1.08 mmol), 4-nitrophenyl azide (178 mg, 1.08 mmol), 4 Å molecular sieves (30 mg) and dioxane (1.5 mL). Reaction time is 24 h. The product was precipitated out in diethyl ether and affording **143** (106 mg, 73% yield) as an off white solid. m.p. 101 ˚C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.21 (sbr, 16H), 3.35 (sbr, 4H), 2.71 (sbr, 16H), 2.60 (sbr, 16H), 2.45 (sbr, 32H), 1.96 - 1.56 (m, 62H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.4, 131.9, 52.2, 50.9, 45.8, 29.8, 27.5, 25.8, 22.8, 22.6, 22.0, 20.2; MS (ESI)+: m/z: 1622 (M^+); HRMS (ESI+): m/z calcd for $C_{88}H_{145}N_30$ $[M+H]^+$: 1622.2262, found 1622.2211.

1-(2-(1*H*-imidazol-4-yl)ethyl)-5-phenyl-1H-1,2,3-triazole (145a): Acetophenone (52 mg, 0.42 mmol), histamine (65 mg, 0.59 mmol), 4-nitrophenyl azide (68 mg, 0.42 mmol), 4 Å molecular sieves (50 mg) and toluene (0.4 mL). Reaction time is 12 h. The product was purified by flash column chromatography (DCM followed by DCM/MeOH = 95:5) affording **145a** (61 mg, 61% yield) as an off-white semi solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.52 (s, 1H), 7.45 - 7.43 (m, 3H), 7.26 - 7.22 (m, 2H), 6.95 (sbr, 1H), 6.64 (s, 1H), 4.61 (t, 2H, J = 7.0 Hz), 3.22 (t, 2H, J = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.5, 135.1, 134.0, 132.9, 129.2, 128.8, 126.8, 116.5, 48.2, 28.1; MS (EI): m/z: 239 (M^+); HRMS (ESI+): m/z calcd for $C_{13}H_{14}N_5$ $[M+H]^+$: 240.1243, found 240.1248.

3-(2-(5-Phenyl-1H-1,2,3-triazol-1-yl)ethyl)-1H-indole (145b): Acetophenone (50 mg, 0.42 mmol), tryptamine (94 mg, 0.59 mmol), 4-nitrophenyl azide (68 mg, 0.42 mmol), acetic acid (8 mg, 0.13 mmol), 4 Å molecular sieves (50 mg) and toluene (0.4 mL). Reaction time is 12 h. The product was purified by flash column chromatography (DCM followed by heptane/EtOAc = 6:4) affording **145b** (90 mg, 75% yield) as an off white solid. m.p. 123 - 124 ˚C. ^{1}H NMR (300 MHz, CDCl3) δ 8.09 (s, 1H), 7.63 (s, 1H), 7.41 - 7.14 (m, 6H), 7.06 - 7.00 (m, 3H), 6.83 (s, 1H), 4.60 (t, 2H, J = 7.3 Hz), 3.33 (t, 2H, J = 7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4, 136.3, 133.0, 129.3, 128.9, 128.8, 127.1, 127.0, 122.6, 122.2, 119.6, 118.2, 111.4, 111.2, 48.8, 26.6; MS (EI): m/z: 288 (M^+); HRMS (ESI+): m/z calcd for $C_{18}H_{17}N_4$ $[M+H]^+$: 289.1445, found 289.1446.

1-(((1S,4aS)-7-Isopropyl-1,4a-dimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-1-yl)methyl)-5- phenyl-1*H*-1,2,3-triazole (145c): Acetophenone (50 mg, 0.42 mmol), dehydroabietylamine (166 mg, 0.58 mmol), 4-nitrophenyl azide (68 mg, 0.42 mmol), acetic acid (8 mg, 0.13 mmol), 4 Å molecular sieves (50 mg) and toluene (0.8 mL). Reaction time is 48 h. The product was purified by flash column chromatography (DCM followed by heptane/EtOAc = 5:5) affording **145c** (132 mg, 76% yield) as an offwhite solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (s, 1H), 7.48 - 7.46 (m, 3H), 7.35 - 7.32 (m, 2H), 7.08 (d,

1H, J = 8.1 Hz), 6.94 (d, 1H, J = 8.1 Hz), 6.87 (s, 1H), 4.32 (s, 2H), 2.86 - 2.76 (m, 3H), 2.19 - 2.15 (m, 1H), 1.80 - 1.31 (m, 6H), 1.22 (s, 3H), 1.20 (s, 3H), 1.15 (s, 3H), 1.05 - 1.04 (m, 2H), 0.93 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.0, 145.8, 139.1, 134.7, 133.1, 129.4, 129.3, 129.2, 128.3, 127.0, 124.1, 123.9, 58.4, 45.9, 39.4, 38.1, 37.7, 36.6, 33.6, 29.9, 25.6, 24.1, 24.0, 19.4, 18.7, 18.5; MS (EI): m/z: 413 (M^+); HRMS (ESI+): m/z calcd for $C_{28}H_{36}N_3$ $[M+H]^+$: 414.2903, found 414.2909.

2-(5-Phenyl-1*H*-1,2,3-triazol-1-yl)octadecane-1,3,4-triol (145d): Acetophenone (50 mg, 0.42 mmol), phytosphingosine (185 mg, 0.58 mmol), 4-nitrophenyl azide (68 mg, 0.42 mmol), 4 Å molecular sieves (50 mg) and toluene (1 mL). Reaction time is 48 h. The product was purified by flash column chromatography (DCM followed by DCM/MeOH = 95:5) affording **145d** (150 mg, 81% yield) as an off white semi-solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (s, 1H), 7.50 - 7.49 (m, 3H), 7.45 - 7.43 (m, 2H), 4.81 - 4.78 (m, 1H), 4.37 - 4.33 (m, 1H), 4.11 - 4.07 (m, 2H), 3.59 - 3.54 (m, 1H), 2.93 (sbr, 1H), 1.38 - 1.08 (m, 26H), 0.88 (t, 3H, J = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.0, 132.8, 130.0, 129.4, 129.3, 126.5, 75.5, 72.3, 62.0, 60.3, 32.1, 29.8, 29.8, 29.8, 29.7, 29.7, 29.5, 25.9, 22.8, 14.2; MS (EI): m/z: 445 (M^+); HRMS (ESI+): m/z calcd for $C_{26}H_{44}N_3O_3$ $[M+H]^+$: 446.3376, found 446.3372.

(6bS,8aS,12aS,12bR)-9-(4-Methoxybenzyl)-8a-methyl-1,2,6b,7,8,8a,9,12,12a,12bdecahydronaphtho[2',1':4,5]indeno[1,2-d][1,2,3]triazol-4-ol (145e1): Estrone (113 mg, 0.42 mmol), 4-methoxybenzylamine (160 mg, 1.18 mmol), 4-nitrophenyl azide (137 mg, 0.84 mmol), acetic acid (8 mg, 0.13 mmol), 4 Å molecular sieves (50 mg) and toluene (1.5 mL). Reaction time is 72 h. The product was purified by flash column chromatography (DCM followed by heptane/EtOAc = 3:7) affording **145e1** (123 mg, 71% yield) as an off white solid. m.p. 210 – 211 ˚C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18 (d, 2H, J = 8.7 Hz), 7.09 (d, 1H, J = 8.7 Hz), 6.86 (d, 2H, J = 8.7 Hz), 6.65 - 6.58 (m, 2H), 5.49 - 5.31 (m, 2H), 5.08 (sbr, 1H), 3.80 (s, 3H), 2.89 - 2.75 (m, 3H), 2.48 - 2.23 (m, 4H), 2.07 - 2.03 (m, 2H), 1.95 - 1.42 (m, 4H), 0.73 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.8, 154.0, 149.3, 138.0, 131.7, 129.2, 127.6, 126.2, 115.6, 114.3, 113.0, 61.7, 55.4, 52.7, 44.1, 41.5,

37.3, 34.0, 29.4, 30 27.4, 25.9, 24.6, 17.2; MS (EI): m/z: 415 (M^+); HRMS (ESI+): m/z calcd for $C_{26}H_{30}N_3O_2$ $[M+H]^+$: 416.2332, found 416.2332.

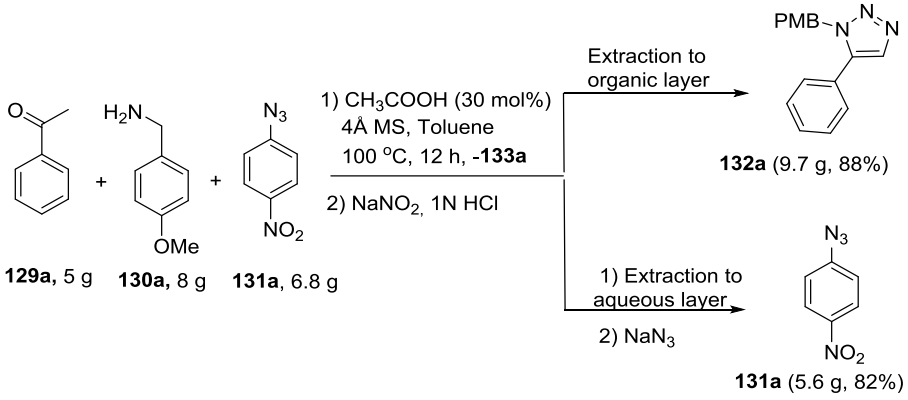
(6bS,8aS, 12aS, 12bR)-9-Butyl-8a-methyl-1,2,6b,7,8,8a,9, 12, 12a, 12b-decahydronaphtho[2', 1':4,5]indeno[1,2-d][1,2,3]triazol-4-ol (145e2): Estrone (113 mg, 0.42 mmol), n-butyl amine (120 mg, 1.66 mmol),4-nitrophenyl azide (137 mg, 0.84 mmol), acetic acid (8 mg, 0.13 mmol), 4 Å molecular sieves (50 mg) and toluene (1.5 mL). Reaction time is 72 h. The product was purified by flash column chromatography (DCM followed by heptane/EtOAc = 3:7) affording **145e2** (130 mg, 88% yield) as an off white solid. m.p. 264 - 265 ˚C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13 (d, 1H, J = 8.6 Hz), 6.70 - 6.66 (m, 1H), 6.62 (s, 1H), 5.61 (sbr, 1H), 4.30 - 4.19 (m, 2H), 2.93 - 2.77 (m, 3H), 2.50 - 2.25 (m, 5H), 1.98 - 1.92 (m, 4H), 1.89 - 1.35 (m, 5H), 1.05 (s, 3H), 0.97 (t, 3H, J = 7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.0, 154.3, 149.2, 138.1, 131.8, 126.2, 115.6, 113.0, 61.7, 49.1, 44.2, 41.4, 37.3, 34.3, 32.8, 29.5, 27.4, 26.0, 24.5, 20.0, 17.9, 13.7; MS (EI): m/z: 351 (M^+); HRMS (ESI+): m/z calcd for $C_{22}H_{30}N_3O$ $[M+H]^+$: 352.2382, found 352.2381.

(1S,3aS,3bR,5aS,10aS,10bS,12aS)-7-(4-Methoxybenzyl)-10a,12a-dimethyl- 1,2,3,3a,3b,4,5,5a,6,7,10,10a,10b,11,12,12a-hexadecahydrocyclopenta[7,8]phenanthro[2,3- d][1,2,3]triazol-1-ol (145f): 5α-Dihydrotestosterone (120 mg, 0.42 mmol), 4-methoxybenzylamine (80 mg, 0.58 mmol), 4-nitrophenyl azide (68 mg, 0.42 mmol), acetic acid (8 mg, 0.13 mmol), 4 Å molecular sieves (50 mg) and toluene (0.8 mL). Reaction time is 12 h. The product was purified by flash column chromatography (DCM followed by heptane/EtOAc = 4:6) affording **145f** (160 mg, 88% yield) as an offwhite solid. m.p. 96 - 97 ˚C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13 (d, 2H, J = 8.5 Hz), 6.86 (d, 2H, J = 8.7 Hz), 5.35 (s, 2H), 3.79 (s, 3H), 3.65 (t, 1H, J = 8.5 Hz), 2.85 (d, 1H, J = 15.6 Hz), 2.40 - 2.24 (m, 2H), 2.09 - 1.83 (m, 3H), 1.72 - 1.22 (m, 11H), 1.15 - 0.85 (m, 4H), 0.75 (s, 3H), 0.66 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.6, 143.8, 130.6, 128.9, 127.1, 114.3, 81.8, 55.4, 53.8, 51.5, 50.9, 42.9, 42.2, 36.8, 36.7, 36.2, 35.6, 31.2, 30.5,

28.9, 24.6, 31 23.5, 20.8, 11.7, 11.2; MS (EI): m/z: 435 (M^+); HRMS (ESI+): m/z calcd for $C_{27}H_{38}N_3O_2$ $[M+H]^+$: 436.2958, found 436.2956.

4.3 **Preparation of *N*- (4-Methoxybenzyl)-1- (4-nitrophenyl)-5-phenyl-4,5-dihydro-1*H*-1,2,3-triazol-5- amine (134):** To an oven-dried screw-capped reaction tube equipped with a magnetic stir bar was added acetophenone (500 mg, 4.2mmol), 4-methoxybenzylamine (800 mg, 5.8 mmol) and 4 Å molecular sieves (500 mg). The mixture was dissolved in anhydrous toluene (4 mL) and stirred at 100 °C for 2 h. After cooling it down to room temperature, an equivalent of 4-nitrophenyl azide (680 mg, 4.2 mmol) was added and the reaction mixture was stirred for another 6 h at 50°C. The resulting reaction mixture was precipitated in diethyl ether, filtered and dried to afford 1.2 g of the triazoline intermediate **134** in 75% yield. m.p. 153 – 154 ˚C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (d, 2H, J = 8.7 Hz), 7.54 – 7.26 (m, 7H), 7.01 (d, 2H, J = 8.2 Hz), 6.79 (d, 2H, J = 8.5 Hz), 4.82 (d, 1H, J = 18 Hz), 4.35 (d, 1H, J = 18.7 Hz), 3.77 (s, 3H), 3.37 (t, 1H, J = 10.9 Hz), 2.96 (d, 1H, J = 12.0 Hz), 2.60 (d, 1H, J = 10.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 144.7, 142.6, 141.5, 130.1, 129.7, 129.6, 129.0, 125.7, 125.6, 114.7, 114.1, 81.6, 80.2, 55.4, 45.9; MS (EI): m/z: 403 (M^+); HRMS (ESI+): m/z calcd for $C_{22}H_{22}N_5O_3$ $[M+H]^+$: 404.1717; found 404.1717.

2.4.3 **Bulk synthesis of 1,2,3-triazole (132a) and the regeneration of the 4-nitrophenyl azide (131a)**



129a, 5 g **130a,** 8 g **131a**, 6.8 g

132a (9.7 g, 88%)

131a (5.6 g, 82%)

To a 250 mL round-bottom flask equipped with a magnetic stir bar was added an equivalent of acetophenone (5 g, 42mmol), 1.4 equivalents of 4-methoxybenzylamine (8 g, 58mmol), one equivalent of 4-nitrophenyl azide (6.8 g, 42mmol), 30 mol% of acetic acid (8 mg, 0.13 mmol) (0.8 mL, 12.6mmol) and 4 Å molecular sieves (5 g). The mixture was dissolved in anhydrous toluene (30 mL) and stirred at 100 °C for 12 hr. The solvent was evaporated off and the resulting reaction mixture was suspended in hydrochloric acid (3N, 100mL) and methanol (30 mL) was added to aid the solubility. After cooling the solution to 0 °C, $NaNO_2$ (6g) in water (20 mL) was added dropwise. The resulting solution was stirred at 0 °C for 30 minutes, after which reaction mixture was extracted with ethyl acetate at 0-5 °C. The aqueous layer was collected separately and the organic fraction was washed with a saturated $NaHCO_3$ 32 solution and brine, dried over $MgSO_4$ and concentrated *in vacuo* to afford 1,5-disubstituted 1,2,3-triazole **132a** (9.7 g) in sufficent purity with an overall yield of 88%. To the aqueous layer, a solution of NaN_3 (4 g) in 20 mL of water was added dropwise at 0 °C and the whole was stirred for at least an hour at room temperature. The reaction mixture was extracted with diethyl ether and the organic fraction was washed with a saturated NaHCO3 solution and brine, dried over $MgSO_4$ and concentrated *in vacuo* to get the desired azide compound **131a** (5.6 g) in sufficient purity (82% yield).

2.5 References

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Chapter 3

A Single-Step Acid Catalyzed reaction for Rapid Assembly of NH-1,2,3-Triazoles

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assembly of NH-1,2,3-triazoles" Joice Thomas, Sampad Jana, Sandra Liekens and Wim Dehaen Chem. Commun., 2016,52, 9236-9239] Copyright © [2016] Royal Society of chemistry
Joice Thomas wrote the manuscript, Sampad Jana carried out the experiments and analyzed the data.

3.1 Introduction

NH-1,2,3-Triazoles are an important class of heterocyclic compounds which are widely used in cutting edge research for various applications that range from drug discovery to advanced materials. The close resemblance of these moieties to amide bonds has been successfully exploited in the discovery of a considerable number of privileged medicinal scaffolds (Fig. 5a–d).[1] In material chemistry, various 5-pyridyl-substituted *1H*-triazolyl moieties have been employed as versatile ligands to synthesize co-ordination complexes for optoelectronic applications.[2] Interestingly, they also serve as key synthetic intermediates for a series of important transformations in organic synthesis. For example, *N-2* functionalization of *NH*-triazoles via alkylation[3a] and arylation[3b,c] was achieved with high regioselectivity and very recently, asymmetric transannulation of *N*-unsubstituted 1,2,3-triazoles with olefins to 2,3-dihydropyrroles was reported by using a chiral dirhodium catalyzed reaction.[3d,e] Moreover, post-functionalization of these building blocks led to the synthesis of various potential antibacterial and anticancer agents (Figure 5e–g).[1e]

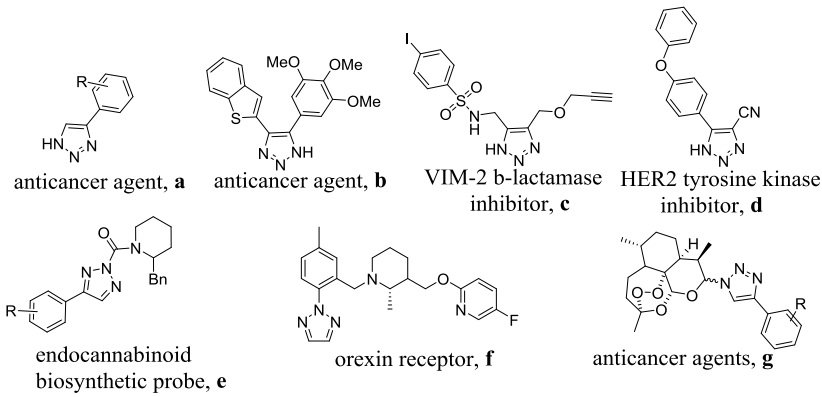


Figure 5 Illustration of pharmaceutically active *NH*-1,2,3-triazoles and *N*-substituted derivatives.

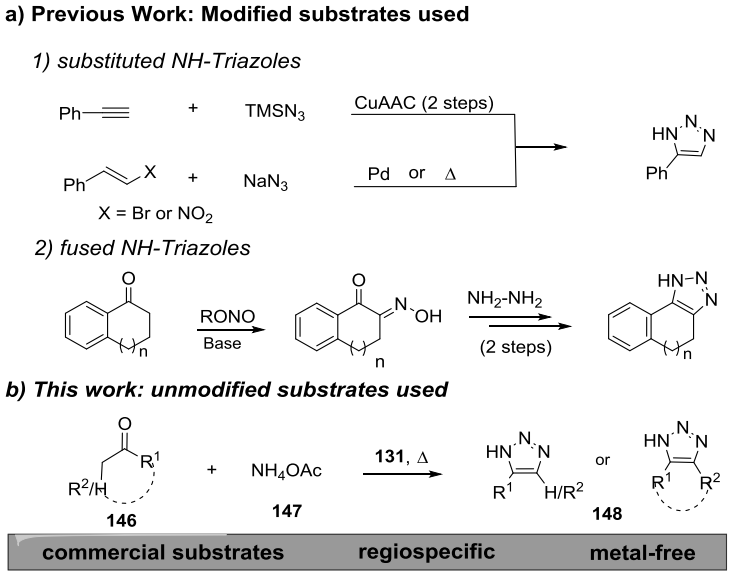


Figure 6 Summary of pre vious[1 & 7] and present work.

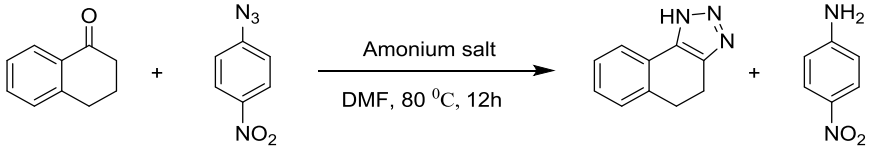
Many selective protocols for synthesizing 1,2,3-triazoles have been developed in the past years, inspired by the Cu- or Ru-catalyzed azide–alkyne cycloaddition (CuAAC or RuAAC) reactions[4] or organocatalytic cycloaddition reactions of azides with enolizable groups.[5] Nevertheless, most of these strategies result in 1,4/1,5- disubstituted-1,2,3-triazoles, and only few yield *NH*-triazoles.[5a] Most of the publicized routes cover the CuAAC reaction of trimethylsilyl azide ($TMSN_3$) and an alkyne followed by the deprotection of the trimethylsilyl group,[1a,e,6c] Pd-catalyzed synthesis of *NH*-triazoles from sodium azide and alkenyl bromides[6f] and 1,3-dipolar cycloaddition of nitroolefins and sodium azide[6d,h] (Figure 6).[6]

3.2 Results and discussions

Despite the progress of metal catalyzed reactions, organocatalytic reactions towards *NH*-1,2,3-triazoles remain underexplored. Moreover, carbocyclic fused *NH*-triazoles are obtained in a multistep manner where hazardous hydrazine is used as one of the reagents

(Figure 6a).[6a] This could explain why fused *NH*-triazoles are not readily available and cannot be obtained from sensitive cyclic ketones. Thus, the development of a novel complementary protocol devoid of these drawbacks, currently represents an important goal in the field of triazole chemistry. Recently, we have developed a general metal-free triazolization route that enables the direct preparation of various 1,2,3-triazoles from readily available building blocks such as primary amines, enolizable ketones and 4-nitrophenyl azide as a renewable source of dinitrogen. Mechanistic studies indicated that the triazoline, which was formed via a [3+2] cycloaddition reaction between **131a** and a transiently generated enamine, is the key synthetic intermediate in this transformation.[7] The triazoline intermediate subsequently undergoes aromatization with the loss of a molecule of 4-nitroaniline **133** via an acid catalyzed pathway leading to the respective triazole in a regiospecific manner. We presume that our new approach towards the synthesis of *NH*-triazoles also follows a similar mechanistic pathway Herein, we disclose the successful implementation of our protocol by the replacement of the primary amine by an ammonium salt resulting in the synthesis of *N*-unsubstituted 1,2,3-triazoles (Figure 6b). Despite the elegance of the other well established methods,[7] the significance of the present chemistry is twofold: (1) the rapid and easy access to *NH*-triazoles in a single step from commercially available ketones. (2) This strategy enables great scaffold diversity in *NH*-triazole skeletons such as 4-substituted, 4,5-disubstituted and very importantly, previously inaccessible or scarcely reported fused *NH*-triazoles in a single step.

We started our study by investigating the triazolization of 1-tetralone **146a**. Among the various ammonium salts (NH_4OH, $(NH_4)_2CO_3$, NH_4OAc and NH_4Cl) and solvents (toluene, ethanol, DMF and DMSO) screened, NH_4OAc and DMF gave the best result. Thus, through the optimization of the appropriate reaction parameters, we were able to develop a method which involves a one-pot reaction of **146a**, **131** and NH_4OAc in a respective molar ratio of 1:1.3:5 in a solution of DMF at 80 °C over a period of 12 h affording *NH*-1,2,3-triazole **148a** with an isolated yield of 87%.



146a **131a** **148a**

entry	Ammonium salts	solvent	Temp (°C)	Time (h)	Yield (%)[a]
1	NH_4OH(1 equiv.)	toluene	80	12	13
2	NH_4CO_3(1 equiv.)	toluene	80	12	18
3	NH_4OAc(1 equiv.)	toluene	80	12	46
4	NH_4Cl(1 equiv.)	toluene	80	12	18
5	NH_4OAc(1 equiv.)	DMF	80	12	62
6	NH_4OAc(1 equiv.)	DMSO	80	12	51
7	NH_4OAc(1 equiv.)	EtOH	80	12	43
8	NH_4OAc(3 equiv.)	DMF	80	12	77
9	NH_4OAc(5 equiv.)	DMF	80	12	86
10	NH_4OAc(6 equiv.)	DMF	80	12	84
11	NH_4OAc(5 equiv.)	DMF	60	24	77
12	NH_4OAc(5 equiv.)	DMF	100	12	81

Table 4 optimization study
[a]Isolated yield

Subsequently, the optimized conditions for the triazolization reaction were applied to a variety of cyclic ketones to synthesize 4,5-fused *NH*-triazoles. Aromatic bicyclic ketone **146b** was compatible with the presented reaction; benzannulated triazole derivative **148b** was obtained as the exclusive product in excellent yield. Interestingly, an array of cyclic ketones containing five to eight carbon atoms gave high yields under the standard conditions (**148c–f**). In order to further highlight the potential applicability of this methodology, azaspinacine derivative **148g** was also synthesized in a single step. This piperidine annulated triazole derivative **148g** could be considered as a ticlopidine analogue (an adenosine diphosphate receptor inhibitor) containing a triazole moiety instead of the thiophene nucleus.[8a] Thus, this single step protocol addresses the previous limitations in triazole chemistry, such as the synthesis of 4,5-fused *NH*-triazoles.

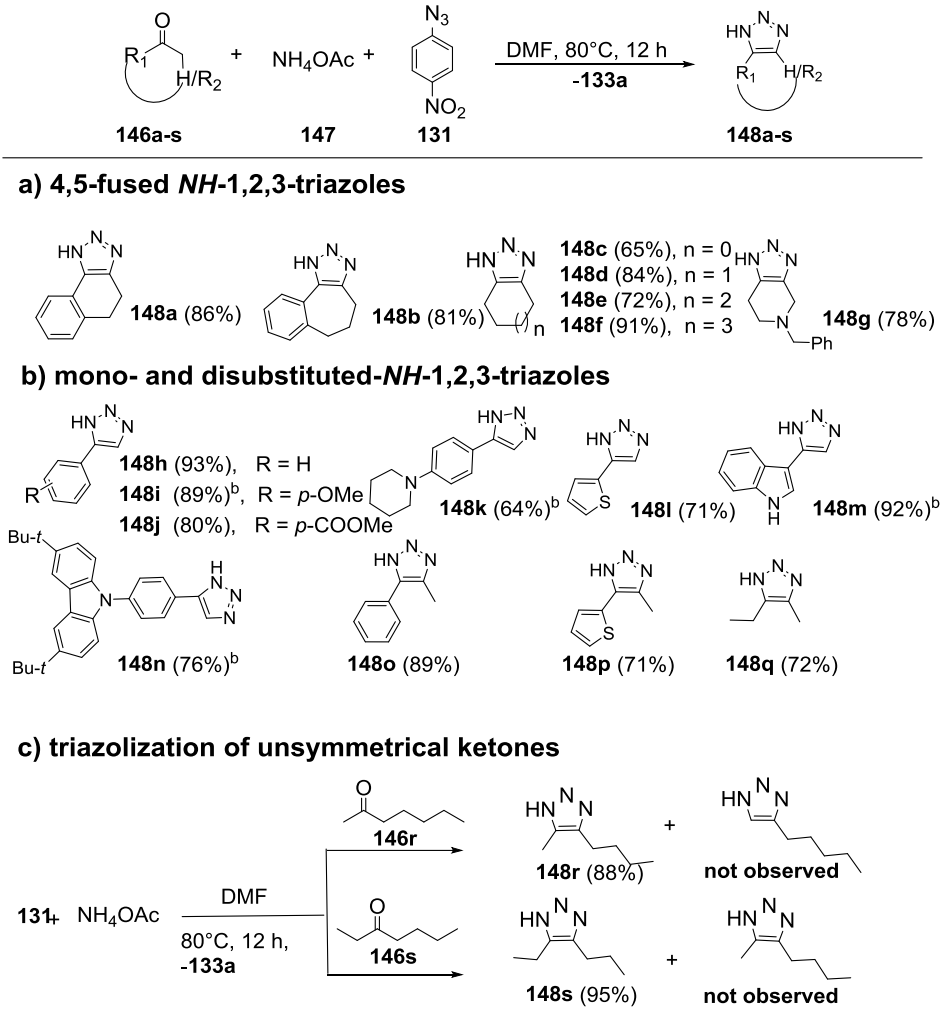


Table 5 Generality of triazole synthesis[a]

[a]Reaction conditions: **146a** (1.0 equiv.), NH_4OAc (5 equiv.), **131a** (1.3 equiv.), DMF (1 mL), 80° C, 12 h, Isolated yield. [b]24 h.

Next, we examined the scope of this protocol towards the synthesis of *N*-unsubstituted 4-aryl-1,2,3-triazoles starting from various substituted acetophenones. In general, all of the examined acetophenones were well tolerated and the desired products were

isolated in excellent yield, regardless of the presence of electron-withdrawing and electron-donating groups on the aromatic rings (**148h–k**). It is noteworthy that heterocyclic moieties such as thiophene, indole and carbazole were amenable to the reaction and afforded the corresponding products in good yields (148l–n). Our interest in skeletal diversity also led us to investigate the synthesis of 4,5-disubstituted 1,2,3-triazoles. Different aryl or alkyl ketones such as aryl propanones or 5-pentanone gave the corresponding disubstituted triazoles (**148o–q**) in good to excellent yield (Table 5a-b).

We then tackled the triazolization of unsymmetrical ketones, with two possible places for enamine formation, in a regiospecific manner. In our previous studies, we observed that the reaction with unsymmetrical 2-ketone and a primary amine gave a mixture of two products with higher preference for the trisubstituted 1,2,3-triazole.[7] Contrary to this observation, the reaction with 2-heptanone **146r** only gave the product derived from the highly substituted enamine **148r**. The relatively acidic conditions and lower steric hindrance of the triazoline adduct of the *NH*-triazole **148r**, as compared to the reaction circumstances with primary amines, explains why only one of two potential enamines and triazoline intermediates forms, which solves the regiochemistry problem. Similarly, the reaction with 3-heptanone **146s** also led to a single product **148s** derived from the thermodynamically more stable enamine (Table 5c).

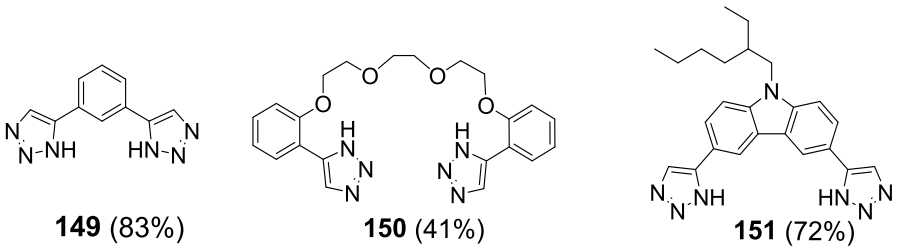


Figure 7 Substrate scope of the multifunctional building blocks.

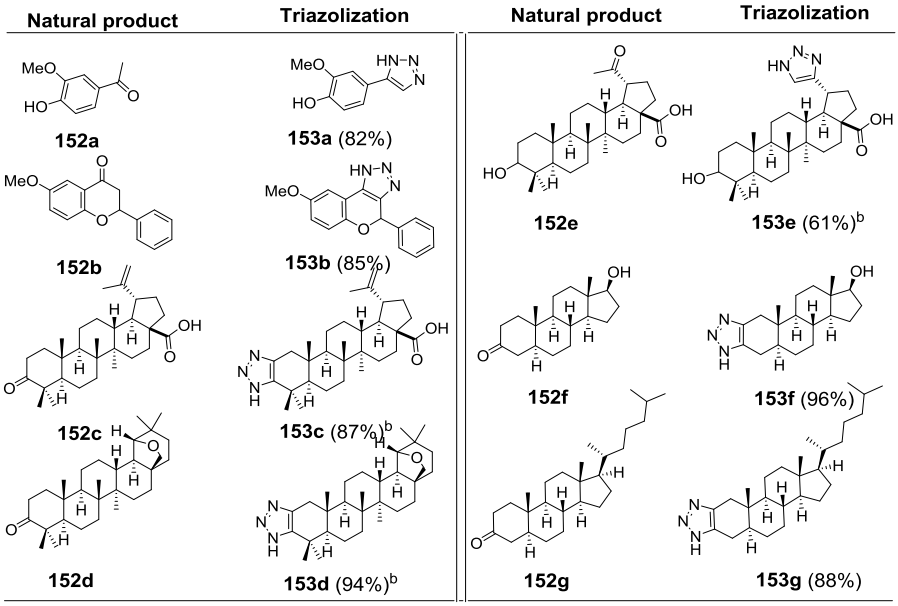


Table 6 Triazolization of natural products[a]

[a]Reaction conditions: **152** (1.0 equiv.), NH_4OAc (5 equiv.), **131a** (1.4 equiv.), DMF (1 mL), 80° C, 12 h, Isolated yield. [b]24 h.

During the last years, many groups have been investigating bis-triazole compounds as potential ligands for various supramolecular applications.[2,8b] To validate the utility of this reaction in designing various receptors in a supramolecular perspective, different bis-*NH*-1,2,3-triazoles [5–7] were synthesized in a single step starting from the corresponding bis-acetyl derivatives (Figure 7). Functionalization of natural products with a triazole nucleus has emerged as an attractive strategy in designing new classes of nature-inspired structural entities with medicinal benefits. These transformations usually require multistep strategies which involve the post-functionalization of the respective natural products with ‘‘clickable’’ alkyne or azido functionalities followed by a metal-catalyzed cycloaddition reaction.[8c] The presented protocol provides a streamlined strategy for the triazolization of dozens of readily available natural products in the search for new drug candidates. Triazolization of acetovanillone **152a** occurred smoothly using our optimized conditions which led to the

expected *NH*-triazole **153a** in good yield. Next, we successfully applied this reaction to the flavonoid-related compound **152b** giving rise to the benzopyran fused triazole **153b** as the sole product. Several terpenoids with fused or tethered triazole heterocycles were proven to have enhanced biological or pharmacological activities as compared to the parent compounds.[1c,f] For example, betulinic acid is a naturally occurring pentacyclic triterpenoid and conjugation with triazoles has been reported to be effective against a variety of cancer cell lines.[8d] In addition, the presence of various fused heterocyclic rings at the C-2 and the C-3 positions of betulinic acid is known to result in diverse potent biological activities.[8e] However, fused 1,2,3-triazole derivatives of these triterpenoids have not been investigated to date. Application of the present methodology to betulonic acid **152c**, the 3-oxo derivative of betulinic acid, which has a 3-OH, led to rapid access to triazole ring-fused derivative **153c**. To show the versatility of this novel approach of triazolization, a number of other terpenes were also converted into the desired *NH*-triazoles with good yields. Notably, the analogous allobetulone **152d** underwent a similar transformation on the A-ring giving rise to the expected product **153d** in excellent yield.[8f] Similarly, the anti-HIV agent platanic acid **152e** also provided the expected product **153e**, in 61% yield.[8g] Next, we addressed the functionalization of the male sex hormone analogue, dihydrotestosterone **152f**, which gave the expected product **153f** in high yield with excellent regioselectivity on the less hindered position. In a similar manner, cholesterol-derived oxysterols, cholestan-3-one **152g** underwent highly selective ring fusion at C2 and C3 carbon, providing **153g** as the only regioisomer.

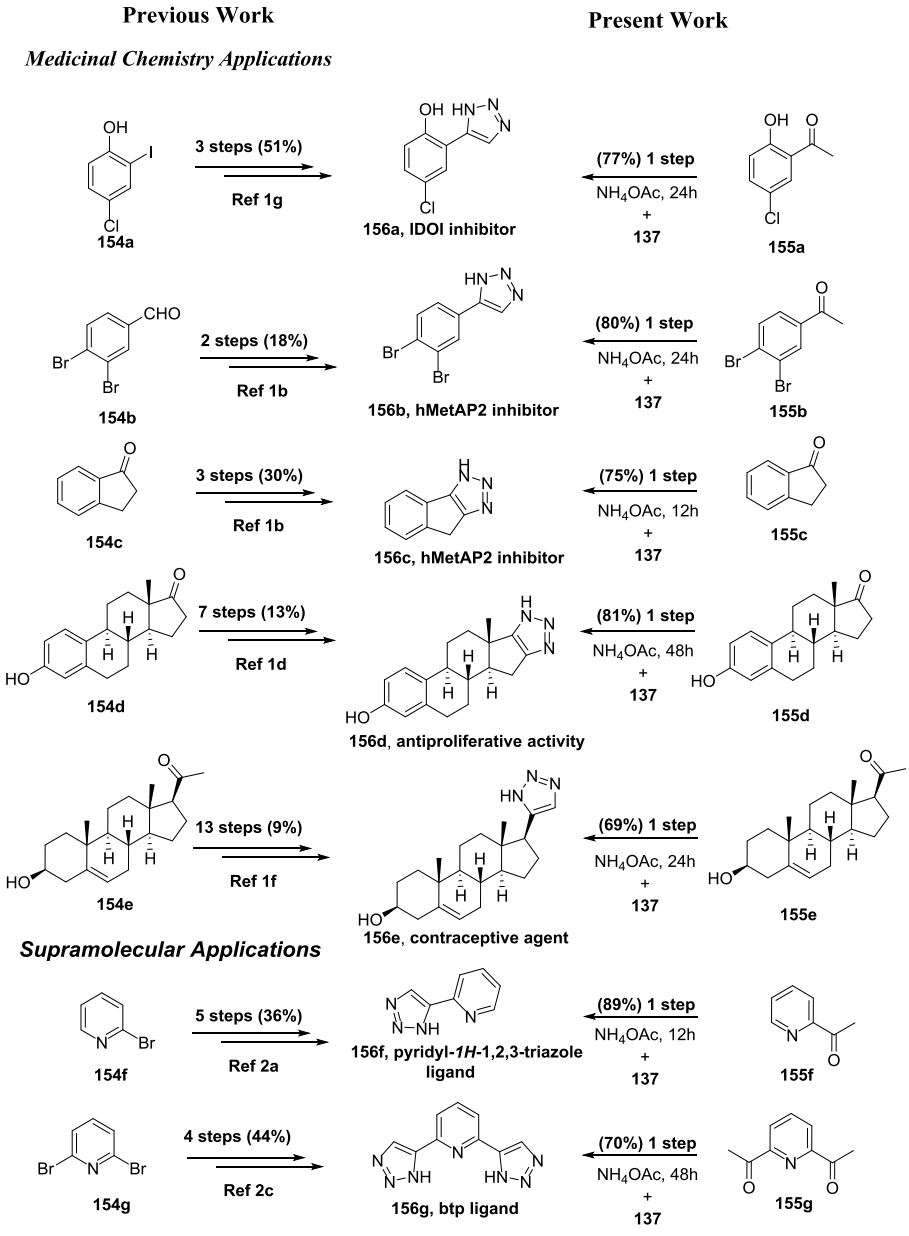


Table 7 Applications towards the synthesis of active pharmaceutical agents and supramolecular receptors

This novel triazolization strategy provides a convenient gateway to synthesize high value *NH*-1,2,3-triazole derivatives which are known to be active pharmaceutical agents, or potential supramolecular receptors in a single step from simple and readily available building blocks. The examples below highlight the synthetic advantages of our new method with respect to selected compounds of interest **156a–g**, the synthesis of which often takes quite a bit of effort. Various commercially available acetophenone derivatives and indanone can be readily converted to the biologically relevant molecules **156a–c** in a single step.[1a,f] Recently, a D-ring-fused *NH*-1,2,3-triazole derivative of estrogen **156d** was reported to have potent antiproliferative activity without affecting healthy cells.[1d] Nevertheless, the downside of this work is the seven-step synthesis to yield the final compound **156d** starting from the parent compound estrone **154d**. Our approach is a truly elegant solution to this issue since we synthesized **156d** in a single step from the same precursor **154d**. Using the new triazolization methodology, we could synthesize an *NH*-triazole derivative of pregnenolone **156e** which was recently identified as a contraceptive agent.[1f] A thirteen-step synthesis using the same starting material **154e** was previously followed for the synthesis of this compound. In a final venture to illustrate the potential efficiency of this strategy, we were able to apply the triazolization process to the synthesis of the well-known bi- and tridentate ligands **156f** and **156g** in a single step from commercially available acetyl pyridines **155f** and **155g**.[2a,c]

3.3 Conclusion

Given the importance of these ligands in supramolecular chemistry for various optoelectronic applications, we trust that this operationally simple strategy will make these materials readily available to the scientific community. In summary, the combination of enolizable ketones, nitrophenyl azide and NH_4OAc is shown to be a powerful method to achieve various mono-, di- or fused *NH*-triazole derivatives, and we expect many future developments using this strategy. Novel and notable features of this tandem reaction include metal-free conditions, regiospecificity, and high functional group tolerance.

Extension of the protocol to the direct conversion of compounds containing multiple keto groups to the corresponding triazole heterocycles in a safe manner is especially notable. Importantly, this new reaction provides an operationally simple pathway for the triazolization of natural products containing enolizable ketone functionalities.

3.4 Experimental Procedures

3.4.1 General procedure for the preparation of substituted *NH*-1,2,3-triazoles

To an oven-dried screw-capped reaction tube equipped with a magnetic stir bar were added the ketone, ammonium acetate, and 4-nitrophenyl azide. The mixture was dissolved in DMF and stirred at 80 °C for 12 - 24 h. Upon completion, the DMF was removed *in vacuo* and purified by column chromatography (silica gel), at first with CH_2Cl_2 as eluent to remove all 4-nitroaniline **4** formed during the reaction followed by using a mixture of heptane and ethyl acetate as eluent to afford the corresponding *NH*-1,2,3-triazole as off-white solids or semi-solids.

3.4.2 Experimental data

4,5-Dihydro-1*H*-naphtho[1,2-d][1,2,3]triazole (148a): Tetralone (69 mg, 0.47 mmol), ammonium acetate (180 mg, 2.35 mmol), 4-nitrophenyl azide (100 mg, 0.61 mmol), and DMF (1 mL). Reaction time was 12 h. The product was purified by flash column chromatography (CH_2Cl_2 followed by heptane/EtOAc = 5:2) afforded **148a** (69 mg, 86% yield) as an off-white solid. m.p. 113 - 114 ˚C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.90 - 7.88 (m, 1H), 7.34 - 7.27 (m, 3H), 3.12 - 3.05 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 144.0, 143.2, 136.2, 128.7, 128.5, 127.5, 127.4, 123.2, 29.2, 20.2. **HRMS** (ESI^+): m/z calcd for $C_{10}H_{10}N_3$ $[M+H]^+$: 172.0869, found 172.0865. Spectroscopic data for **3a** are consistent with previously reported data for the compound.[1]

1,4,5,6-Tetrahydrobenzo[3,4]cyclohepta[1,2-d][1,2,3]triazole (148b): 6,7,8,9-Tetrahydro-5*H*-benzo[7]annulen-5-one (75 mg, 0.47 mmol), ammonium acetate (180 mg, 2.35 mmol), 4-nitrophenyl azide (100 mg, 0.61 mmol), and DMF (1 mL). Reaction time is 12 h. The product was purified by flash column chromatography (CH_2Cl_2 followed by heptane/EtOAc = 5:2) afforded **148b** (70 mg, 81% yield) as an off-white solid. m.p. 173 - 174 ˚C. **^{1}H NMR** (400 MHz, MeOD) δ 7.91 (d, *J* = 7.6 Hz, 1H), 7.19 – 7.07 (m, 3H), 2.96 (t, *J* = 6.7 Hz, 2H), 2.80 (t, *J* = 5.3 Hz, 2H), 1.97 – 1.91 (m, 2H). **^{13}C NMR** (100 MHz, MeOD) δ 141.9, 130.9, 130.0, 129.0, 127.6, 36.2, 26.6, 25.2. **HRMS** (ESI^+): m/z calcd for $C_{11}H_{11}N_3$ $[M+H]^+$: 186.1025, found 186.1033.

1,4,5,6-Tetrahydrocyclopenta[d][1,2,3]triazole (148c): Cyclopentanone (40 mg, 0.47 mmol), ammonium acetate (180 mg, 2.35 mmol), 4-nitrophenyl azide (100 mg, 0.61 mmol), and DMF (1 mL). Reaction time was 12 h. The product was purified by flash column chromatography (CH_2Cl_2 followed by heptane/EtOAc = 4:6) afforded **148c** (34 mg, 65% yield) as a colorless solid. m.p. 141 - 142 ˚C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.81 (t, *J* = 7.4 Hz, 4H), 2.62 - 2.52 (m, 2H). **^{13}C NMR** (100 MHz, MeOD) δ 156.1, 29.4, 22.1. **HRMS** (ESI+): m/z calcd for $C_5H_7N_3$ $[M+H]^+$: 110.0712, found 110.0725.

4,5,6,7-Tetrahydro-1*H*-benzo[d][1,2,3]triazole (148d): Cyclohexanone (46 mg, 0.47 mmol), ammonium acetate (180 mg, 2.35 mmol), 4-nitrophenyl azide (100 mg, 0.61 mmol), DMF (1 mL). Reaction time is 12 h. The product was purified by flash column chromatography (DCM followed by hexane/EtOAc = 5:2) afforded **148d** (48 mg, 84% yield) as a colorless solid. m.p. 77 - 78 ˚C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 2.76 (s, 4H), 1.86 (s, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 142.5, 142.4, 23.2, 21.6. **HRMS** (ESI^+): m/z calcd for $C_6H_{10}N_3$ $[M+H]^+$: 124.0869, found 124.0867.

1,4,5,6,7,8-Hexahydrocyclohepta[d][1,2,3]triazole (148e): Cycloheptanone (53 mg, 0.47 mmol), ammonium acetate (180 mg,

2.35 mmol), 4-nitrophenyl azide (100 mg, 0.61 mmol), and DMF (1 mL). Reaction time is 12 h. The product was purified by flash column chromatography (CH_2Cl_2 followed by heptane/EtOAc = 4:6) afforded **148e** (47 mg, 72% yield) as a colorless solid. m.p. 83 - 84 ˚C. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 2.85 (t, *J* = 5.4 Hz, 4H), 1.89 – 1.85 (m, 2H), 1.73 – 1.69 (m, 4H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 146.6, 31.5, 27.5, 26.6. **HRMS** (ESI+): m/z calcd for $C_7H_{11}N_3$ $[M+H]^+$: 138.1025, found 138.1018.

4,5,6,7,8,9-Hexahydro-1*H*-cycloocta[d][1,2,3]triazole (148f): Cyclooctanone (60 mg, 0.47 mmol), ammonium acetate (180 mg, 2.35 mmol), 4-nitrophenyl azide (100 mg, 0.61 mmol), and DMF (1 mL). Reaction time is 12 h. The product was purified by flash column chromatography (CH_2Cl_2 followed by heptane/EtOAc = 4:6) afforded **148f** (65 mg, 91% yield) as a colorless semi-solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.89 (t, *J* = 6.4 Hz, 4H), 1.76 (s_{br}, 4H), 1.48 (s_{br}, 4H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 143.8, 28.3, 25.5, 23.4. **HRMS** (ESI+): m/z calcd for $C_8H_{13}N_3$ $[M+H]^+$: 152.1182, found 152.1187.

5-Benzyl-4,5,6,7-tetrahydro-1*H*-[1,2,3]triazolo[4,5-c]pyridine (148g): 1-benzylpiperidin-4-one (88 mg, 0.47 mmol), ammonium acetate (180 mg, 2.35 mmol), 4-nitrophenyl azide (100 mg, 0.61 mmol), and DMF (1 mL). Reaction time is 12 h. The product was purified by flash column chromatography (CH_2Cl_2 followed by heptane/EtOAc = 1:1) afforded **148g** (78 mg, 78% yield) as an off white solid. m.p. 245 - 246 ˚C. **^{1}H NMR** (300 MHz, MeOD) δ 7.40 – 7.26 (m, 5H), 3.78 (s, 2H), 3.63 (s, 2H), 2.89 - 2.81(m, 4H). **^{13}C NMR** (75 MHz, MeOD) δ 141.2, 139.8, 138.7, 130.5, 129.5, 128.6, 62.7, 51.2, 49.9, 22.5. **HRMS** (ESI+): m/z calcd for $C_{12}H_{14}N_4$ $[M+H]^+$: 215.1291, found 215.1290.

5-Phenyl-1*H*-1,2,3-triazole (148h): Acetophenone (56 mg, 0.47 mmol), ammonium acetate (180 mg, 2.35 mmol), 4-nitrophenyl azide (100 mg, 0.61 mmol), and DMF (1 mL). Reaction time is 12 h. The product was

purified by flash column chromatography (DCM followed by heptane/EtOAc = 5:2) afforded **148h** (62 mg, 93% yield) as an off-white solid. m.p. 148 - 149 ˚C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.8 (s, 1H), 7.85 - 7.82 (m, 2H), 7.49 - 7.36 (m, 3H). **^{13}C NMR** (75 MHz, DMSO-d_6) δ 147.5, 129.9, 129.1, 128.9, 126.3. **HRMS** (ESI$^+$): m/z calcd for $C_8H_8N_3$ $[M+H]^+$: 146.0713, found 146.0716. Spectroscopic data for **3h** are consistent with previously reported data for the compound.[2]

5-(4-Methoxyphenyl)-1*H*-1,2,3-triazole (148i): 1-(4-methoxyphenyl)ethan-1-one (71 mg, 0.47 mmol), ammonium acetate (180 mg, 2.35 mmol), 4-nitrophenyl azide (100 mg, 0.61 mmol), and DMF (1 mL). Reaction time is 24 h. The product was purified by flash column chromatography (CH_2Cl_2 followed by heptane/EtOAc = 4:6) afforded **148i** (73 mg, 89% yield) as an off white semi-solid. m.p. 162 - 163 ˚C. **^{1}H NMR** (300 MHz, MeOD) δ 8.03 (s, 1H), 7.74 (d, *J* = 8.8 Hz, 2H), 6.99 (d, *J* = 8.8 Hz, 2H), 3.38 (s, 3H). **^{13}C NMR** (75 MHz, MeOD) δ 161.4, 128.3, 123.5, 115.4, 55.7. **HRMS** (ESI+): m/z calcd for $C_9H_9N_3O$ $[M+H]^+$: 176.0818, found: 176.0827.

Methyl 4-(1*H*-1,2,3-triazol-5-yl)benzoate (148j): Methyl 4-acetylbenzoate (83mg, 0.47 mmol), ammonium acetate (180 mg, 2.35 mmol), 4-nitrophenyl azide (100 mg, 0.61 mmol), and DMF (1 mL). Reaction time is 12 h. The product was purified by flash column chromatography (CH_2Cl_2 followed by heptane/EtOAc = 4:6) afforded **148j** (75 mg, 80% yield) as an off white solid. m.p. 197.5 – 198.5 ˚C. **^{1}H NMR** (300 MHz, MeOD) δ 8.27 (s, 1H), 8.09 (d, *J* = 8.4 Hz, 2H), 7.97 (d, *J* = 8.4 Hz, 2H), 3.92 (s, 3H). **^{13}C NMR** (100 MHz, MeOD) δ 168.1, 136.2, 131.2, 131.0, 126.7, 52.7; **HRMS** (ESI+): m/z calcd for $C_{10}H_9N_3O_2$ $[M+H]^+$: 204.0767, found: 204.0770.

1-(4-(1*H*-1,2,3-Triazol-5-yl)phenyl)piperidine (148k): 1-(4-(piperidin-1-yl)phenyl)ethan-1-one (95 mg, 0.47 mmol), Ammonium acetate (180 mg, 2.35 mmol), 4-nitrophenyl azide (100 mg, 0.61 mmol), and DMF (1

mL). Reaction time is 24 h. The product was purified by flash column chromatography (CH_2Cl_2 followed by heptane/EtOAc = 1:1) afforded **148k** (68 mg, 64% yield) as an off white solid. m.p. 222 - 223 ˚C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.09 (s, 1H), 7.67 (d, *J* = 8.4 Hz, 2H), 6.97 (d, *J* = 8.6 Hz, 2H), 3.18 (S_{br}, 4H), 1.61 – 1.58 (m, 6H). **^{13}C NMR** (75 MHz, DMSO-d_6) δ 151.3, 146.6, 129.9, 126.5, 126.1, 115.6, 49.1, 25.1, 23.9. **HRMS** (ESI+): m/z calcd for $C_{13}H_{16}N_4$ $[M+H]^+$: 229.1447, found 229.1435.

5-(Thiophen-2-yl)-1*H*-1,2,3-triazole (148l): 1-(thiophen-2-yl)ethan-1-one (60 mg, 0.47 mmol), ammonium acetate (180 mg, 2.35 mmol), 4-nitrophenyl azide (100 mg, 0.61 mmol), and DMF (1 mL). Reaction time is 12 h. The product was purified by flash column chromatography (CH_2Cl_2 followed by heptane/EtOAc = 4:6) afforded **148l** (51 mg, 71% yield) as an off white semi-solid. m.p. 67 - 68 ˚C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.44 – 7.43 (m, 1H), 7.36 – 7.34 (m, 1H), 7.12 – 7.09 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 142.5, 132.1, 129.0, 127.9, 126.0, 125.3. **HRMS** (ESI+): m/z calcd for $C_6H_5N_3S$ $[M+H]^+$: 152.02769**,** found: 152.0276.

3-(1*H*-1,2,3-Triazol-5-yl)-1H-indole (148m): 1-(1H-indol-3-yl)ethan-1-one (74 mg, 0.47 mmol), ammonium acetate (180 mg, 2.35 mmol), 4-nitrophenyl azide (100 mg, 0.61 mmol), and DMF (1 mL). Reaction time is 24 h. The product was purified by flash column chromatography (CH_2Cl_2 followed by heptane/EtOAc = 4:6) afforded **148m** (80 mg, 92% yield) as an off white solid. m.p. 197.5 – 198.5 ˚C. **^{1}H NMR** (300 MHz, MeOD) δ 8.06 (s, 1H), 7.95 (d, *J* = 7.5 Hz, 1H), 7.70 (s, 1H), 7.43 (d, *J* = 7.9 Hz, 1H), 7.22 – 7.12 (m, 2H). **^{13}C NMR** (75 MHz, MeOD) δ 138.2, 126.3, 126.2, 124.4, 123.2, 121.1, 120.52, 112.6. **HRMS** (ESI+): m/z calcd for $C_{10}H_8N_4$ $[M+H]^+$: 185.08216, found:185.0828.

9-(4-(1*H*-1,2,3-Triazol-5-yl)phenyl)-3,6-di-tert-butyl-9*H*-carbazole (148n): 1-(4-(3, 6-di-tert-butyl-9H-carbazol-9-yl) phenyl) ethan-1-one (186 mg, 0.47 mmol), ammonium acetate (180 mg, 2.35 mmol), 4-nitrophenyl azide (100 mg, 0.61 mmol), and DMF (1 mL). Reaction time is 24 h. The product was purified by flash column chromatography (CH_2Cl_2 followed by heptane/EtOAc = 6:4) afforded **148n** (150 mg, 76% yield) as an off white solid. m.p. 130 - 131 ˚C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.15 (s, 2H), 8.06 (t, *J* = 8.4 Hz, 3H), 7.66 (d, *J* = 8.5 Hz, 2H), 7.48 – 7.38 (m, 4H), 1.46 (s, 18 h). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 146.8, 143.2, 139.1, 138.7, 129.6, 128.4, 127.6, 127.2, 123.8, 123.6, 116.4, 109.3, 34.9, 32.1. **HRMS** (ESI$^+$): m/z calcd for $C_{28}H_{30}N_4$ $[M+H]^+$: 423.2543, found 423.2527.

4-Methyl-5-phenyl-1*H*-1,2,3-triazole (148o): propiophenone (62 mg, 0.47 mmol), ammonium acetate (180 mg, 2.35 mmol), 4-nitrophenyl azide (100 mg, 0.61 mmol), and DMF (1 mL). Reaction time is 12 h. The product was purified by flash column chromatography (CH_2Cl_2 followed by heptane/EtOAc = 6:4) afforded **148o** (65 mg, 89% yield) as an off white solid. m.p. 142.5 – 143.5 ˚C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 7.3 Hz, 2H) 7.47 (t, *J* = 7.8 Hz, 2H), 7.39 (t, *J* = 7.4 Hz, 1H), 2.55 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 130.8, 128.9, 128.3, 127.4, 11.7. **HRMS** (ESI+): m/z calcd for $C_9H_9N_3$ $[M+H]^+$: 160.0869, found 160.0873.

4-Methyl-5-(thiophen-2-yl)-1*H*-1,2,3-triazole (148p): 1-(thiophen-2-yl)propan-1-one (66 mg, 0.47 mmol), ammonium acetate (180 mg, 2.35 mmol), 4-nitrophenyl azide (100 mg, 0.61 mmol), and DMF (1 mL). Reaction time is 12 h. The product was purified by flash column chromatography (CH_2Cl_2 followed by heptane/EtOAc = 4:6) afforded **148p** (55 mg, 71% yield) as an off white semi-solid. m.p. 155 - 156 ˚C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.38 – 7.36 (m, 2H), 7.15 – 7.12 (m, 1H), 2.56 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 132.9, 127.8, 125.8, 125.3,

11.3. **HRMS** (ESI+): m/z calcd for $C_7H_7N_3S$ $[M+H]^+$: 166.04334, found: 166.0435.

4-Ethyl-5-methyl-1*H*-1,2,3-triazole (148q) pentan-3-one (40 mg, 0.47 mmol), ammonium acetate (180 mg, 2.35 mmol), 4-nitrophenyl azide (100 mg, 0.61 mmol), and DMF (1 mL). Reaction time is 12 h. The product was purified by flash column chromatography (CH_2Cl_2 followed by heptane/EtOAc = 6:4) afforded **148q** (38 mg, 72% yield) as a colorless semi-solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 2.73 – 2.66 (m, 2H), 2.31(s, 3H), 1.30 – 1.25(t, *J* = 7.6 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 145.4, 139.4, 17.8, 13.4, 9.6. **HRMS** (ESI+): m/z calcd for $C_5H_9N_3$ $[M+H]^+$: 112.0869, found 112.0860.

4-Butyl-5-methyl-1*H*-1,2,3-triazole (148r): heptan-2-one (53 mg, 0.47 mmol), ammonium acetate (180 mg, 2.35 mmol), 4-nitrophenyl azide (100 mg, 0.61 mmol), and DMF (1 mL). Reaction time is 12 h. The product was purified by flash column chromatography (CH_2Cl_2 followed by heptane/EtOAc = 4:6) afforded **148r** (57 mg, 88% yield) as an off white semi-solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 2.67 (t, *J* = 7.8 Hz, 2H), 2.30 (s, 3H), 1.67 – 1.61 (m, 2H), 1.37 – 1.32 (m, 2H), 0.94 - 0.89 (m, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 143.9, 139.4, 31.2, 24.0, 22.4, 13.9, 9.6. **HRMS** (ESI+): m/z calcd for $C_7H_{13}N_3$ $[M+H]^+$: 140.11821, found: 140.1190.

5-Ethyl-4-propyl-1*H*-1,2,3-triazole (148s): heptan-3-one (53 mg, 0.47 mmol), ammonium acetate (180 mg, 2.35 mmol), 4-nitrophenyl azide (100 mg, 0.61 mmol), and DMF (1 mL). Reaction time is 12 h. The product was purified by flash column chromatography (CH_2Cl_2 followed by heptane/EtOAc = 6:4) afforded **148s** (62 mg, 95% yield) as a colorless semi-solid. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 2.73 – 2.62 (m, 4H), 1.76 – 1.64 (m, 2H), 1.29 (t, *J* = 7.6 Hz, 3H), 0.96 (t, *J* = 7.4 Hz, 3H). **^{13}C**

NMR (150 MHz, $CDCl_3$) δ 145.3, 143.6, 26.4, 22.6, 17.9, 13.9, 13.7. **HRMS** (ESI+): m/z calcd for $C_7H_{13}N_3$ $[M+H]^+$: 140.1182, found 140.1196.

1,3-Di(1*H*-1,2,3-triazol-5-yl)benzene (149): 1,3-diacetylbenzene (76 mg, 0.46 mmol), ammonium acetate (360 mg, 4.70 mmol), 4-nitrophenyl azide (200 mg, 1.2 mmol), and DMF (1 mL). Reaction time is 48 h. The product was purified by flash column chromatography (CH_2Cl_2 followed by heptane/EtOAc = 6:4) afforded **149** (mg, 83% yield) as an off white solid. m.p. 238 - 239 ˚C. **^{1}H NMR** (400 MHz, DMSO - d_6) δ 8.45 (s, 2H), 8.40 (s, 2H), 7.88 – 7.86 (m, 2H), 7.57 (t, *J* = 7.7 Hz, 1H). **^{13}C NMR** (100 MHz, DMSO - d_6) δ 162.3, 145.2, 131.1, 129.6, 125.2, 122.6. **HRMS** (ESI+): m/z calcd for $C_{10}H_8N_6$ $[M+H]^+$: 213.08831, found: 213.0887.

1,2-Bis(2-(2-(1*H*-1,2,3-triazol-5-yl)phenoxy)ethoxy)ethane (150): 1,1'-((((ethane-1,2-diylbis(oxy))bis(ethane-2,1-diyl))bis(oxy))bis(2,1-phenylene))bis(ethan-1-one) (80 mg, 0.20 mmol), ammonium acetate (158 mg, 2 mmol), 4-nitrophenyl azide (90 mg, 0.56 mmol), and DMF (1 mL). Reaction Temperature 60˚C, and Reaction time is 4 d. The product was purified by flash column chromatography (CH_2Cl_2 followed by heptane/EtOAc = 1:4) afforded **150** (36 mg, 41% yield) as an off white oily liquid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7:85 (s, 2H), 7.45 (d, *J* = 7.6 Hz, 2H), 7.26 – 7.21 (m, 2H), 7.00 – 6.95 (m, 2H), 6.85 (d, *J* = 8.2 Hz, 2H), 4.17 – 4.13 (m, 4H), 4.06 (s, 4H), 4.00 – 3.97 (m, 4H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 162.7, 154.7, 133.8, 130.0, 127.8, 121.9, 113.7, 70.3, 69.2, 67.4. **HRMS** (ESI+): m/z calcd for $C_{22}H_{24}N_6O_4$ $[M+H]^+$: 437.19316, found: 437.1922.

9-(2-Ethylhexyl)-3,6-di(1*H*-1,2,3-triazol-5-yl)-9H-carbazole (151): 1,1'-(9-(2-ethylhexyl)-9H-carbazole-3,6-diyl)bis(ethan-1-one) (121 mg, 0.335 mmol), ammonium acetate (257 mg, 3.35 mmol), 4-nitrophenyl azide (139 mg, 0.84 mmol), and DMF (1 mL). Reaction time is 48 h. The product was purified by flash column chromatography (CH_2Cl_2

followed by heptane/EtOAc = 4:6) afforded **151** (99 mg, 72% yield) as an off white solid. m.p. 94 - 95 ˚C. **^{1}H NMR** (300 MHz, DMSO-d_6) δ 8.74 (s, 2H), 8.37 (s, 2H), 8.01 – 7.98 (m, 2H), 7.67 (d, *J* = 8.6 Hz, 2H), 4.31 (d, *J* = 7.4 Hz, 2H), 1.37 – 1.14 (m, 9H), 0.87 (t, J = 7.3 Hz, 3H) – 0.78 (t, J = 7.3 Hz, 3H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 162.3, 146.1, 140.7, 124.0, 122.4, 121.5, 117.7, 110.1, 46.7, 38.7, 30.2, 28.0, 23.7, 22.5, 13.8, 10.7. **HRMS** (ESI+): m/z calcd for $C_{24\ h27}N_7$ $[M+H]^+$: 414.24005, found 414.2405.

2-Methoxy-5-(1*H*-1,2,3-triazol-5-yl)phenol (153a): 1-(3-hydroxy-4-methoxyphenyl)ethan-1-one (78 mg, 0.47 mmol), ammonium acetate (180 mg, 2.35 mmol), 4-nitrophenyl azide (100 mg, 0.61 mmol), and DMF (1 mL). Reaction time is 24 h. The product was purified by flash column chromatography (CH_2Cl_2 followed by heptane/EtOAc = 4:6) afforded **153a** (74 mg, 82% yield) as an off white solid. m.p. 156 – 157 ˚C. **^{1}H NMR** (300 MHz, DMSO - d_6) δ 8.18 (s, 1H), 7.39 (s, 1H), 7.26 (d, *J* = 8.1 Hz, 1H), 6.83 (d, *J* = 8.1 Hz, 1H), 3.83 (s, 3H). **^{13}C NMR** (75 MHz, DMSO - d_6) δ 148.0, 146.8, 118.5, 115.8, 109.7, 55.7. **HRMS** (ESI+): m/z calcd for $C_9H_9N_3O_2$ $[M+H]^+$: 192.07674, found 192.0761.

8-Methoxy-4-phenyl-1,4-dihydrochromeno[3,4-d][1,2,3]triazole (153b): 6-methoxy-2-phenylchroman-4-one (119 mg, 0.47 mmol), ammonium acetate (180 mg, 2.35 mmol), 4-nitrophenyl azide (100 mg, 0.61 mmol), and DMF (1 mL). Reaction time is 12 h. The product was purified by flash column chromatography (CH_2Cl_2 followed by heptane/EtOAc = 6:4) afforded **153b** (112 mg, 85% yield) as an off white solid. m.p. 175 - 176 ˚C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.47 – 7.31(m, 6H), 7.00 (d, *J* = 8.9 Hz, 1H), 6.87 – 6.83 (m, 1H), 6.52 (s, 1H), 3.82 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 155.0, 147.6, 142.8, 139.5, 138.6, 129.0, 128.8, 127.2, 118.9, 117.2, 116.3, 107.2, 75.9, 57.0. **HRMS** (ESI+): m/z calcd for $C_{16}H_{13}N_3O_2$ $[M+H]^+$: 280.1080, found 280.1075.

(1R,3aS,5aR,5bR,7aR,12aR,12bR,14aR,14bR)-5a,5b,8,8,12a-Pentamethyl-1-(prop-1-en-2-yl)-2,3,4,5,5a,5b,6,7,7a,8,9,12,12a,12b,13,14,14a,14b-octadecahydrocyclopenta[7,8]chryseno[2,3-d][1,2,3]triazole-3a(1H)-carboxylic acid (153c): Betulonic acid (213 mg, 0.47 mmol), ammonium acetate (180 mg, 2.35 mmol), 4-nitrophenyl azide (100 mg, 0.61 mmol), and DMF (1 mL). Reaction time is 24 h. The product was purified by flash column chromatography (CH_2Cl_2 followed by heptane/EtOAc = 2:8) affording **153c** (195 mg, 87% yield) as an off-white solid. m.p. 146 - 147 ˚C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 4.76 (s, 1H), 4.63 (s, 1H), 3.06 - 2.87 (m, 2H), 2.33 - 1.98 (m, 6H), 1.79 (s, 3H), 1.71 - 1.43 (m, 14H), 1.31 - 1.29 (m, 4H), 1.20 – 1,22 (m, 4H), 1,01 (s, 3H), 0.99 (s, 3H), 0.78 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 181.0, 150.6, 149.3, 139.9, 109.8, 56.5, 53.6, 49.3, 49.2, 47.0, 42.6, 40.9, 39.2, 38.5, 37.4, 37.2, 33.4, 32.3, 31.0, 30.7, 29.9, 25.6, 23.8, 21.5, 19.5, 19.3, 16.4, 15.8, 14.8. **HRMS** (ESI^+): m/z calcd for $C_{30}H_{46}N_3O_2$ $[M+H]^+$: 480.3584; found 480.3580.

(1R,4aR,6aR,6bR,8aR,13aR,13bR,15aR,15bR)-2,2,6a,6b,9,9,13a-heptamethyl-1,2,3,4,5,6,6a,6b,7,8,8a,9,10,13,13a,13b,14,15,15a,15b-icosahydro-1,4a-(epoxymethano)piceno[2,3-d][1,2,3]triazole (153d): Allobetulone (206 mg, 0.47 mmol), ammonium acetate (180 mg, 2.35 mmol), 4-nitrophenyl azide (100 mg, 0.61 mmol), and DMF (1 mL). Reaction time is 24 h. The product was purified by flash column chromatography (CH_2Cl_2 followed by heptane/EtOAc = 4:6) afforded **153d** (204 mg, 94% yield) as an off white solid. m.p. above 300 ˚C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.81 (d, *J* = 7.2 Hz, 1H), 3.58 (s, 1H), 3.47 (d, *J* = 7.8 Hz, 1H), 2.94 (d, *J* = 15.5 Hz, 1H), 2.16 (d, *J* = 15.5 Hz, 1H), 1.61 – 1.56 (m, 6H), 1.53 – 1.50 (m, 4H), 1.49 – 1.42 (m, 3H), 1.39 – 1.32 (m, 7H), 1.29 – 1.23 (m, 5H), 1.19 – 1.55(m, 1H), 1.04 (s, 3H), 0.95 (d, *J* = 2.4 Hz, 6H), 0.82 (s, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 149.8, 140.3, 88.1, 71.4, 53.7, 49.8, 46.9, 41.6, 40.9, 40.8, 39.2, 37.7, 36.8, 36.4, 34.4,

33.5, 33.0, 32.8, 31.2, 29.0, 26.6, 26.5, 26.3, 24.7, 23.9, 21.6, 19.2, 16.7, 15.5, 13.6. **HRMS** (ESI+): m/z calcd for $C_{30}H_{47}N_3O$ $[M+H]^+$: 466.3791 , found 466.3799.

(1R,3aS,5aR,5bR,9S,11aR)-9-hydroxy-5a,5b,8,8,11a-pentamethyl-1-(1H-1,2,3-triazol-5-yl)icosahydro-3aH-cyclopenta[a]chrysene-3a-carboxylic acid (153e): Platanic acid (215 mg, 0.47 mmol), ammonium acetate (180 mg, 2.35 mmol), 4-nitrophenyl azide (100 mg, 0.61 mmol), and DMF (1 mL). Reaction time is 24 h. The product was purified by flash column chromatography (CH_2Cl_2 followed by heptane/EtOAc = 4:6) afforded **153e** (139 mg, 61% yield) as an off white solid. m.p. above 300 ˚C. **^{1}H NMR** (400 MHz, DMSO – d_6) δ 7.57(s, 1H), 4.23 (d, *J* = 4.9 Hz, 1H), 3.62 – 3.57 (m, 1H), 2.96 – 2.89 (m, 1H), 2.24 – 2.03 (m, 3H), 1.90 – 1.82 (m, 2H), 1.76 – 1.67 (m, 1H), 1.50 – 1.41 (m, 7H), 1.33 – 1.31 (m, 2H), 1.18 – 1.05 (m, 5H), 0.89 (s, 3H), 0.86 (s, 6H), 0.81 – 0.76 (m, 1H), 0.73 (s, 3H), 0.64 (s, 3H), 0.61 – 0.59 (m, 1H), 0.46 – 0.43 (m, 1H). **^{13}C NMR** (100 MHz, DMSO-d_6 + TFA, 1drop) δ 177.7, 150.5, 127.4, 77.4, 55.9, 55.3, 53.7, 50.1, 42.3, 40.6, 38.7, 37.9, 37.1, 35.1, 34.3, 33.0, 29.6, 28.4, 27.4, 26.6, 20.8, 18.3, 16.2, 16.1, 16.1, 14.6. **HRMS** (ESI+): m/z calcd for $C_{29}H_{45}N_3O_3$ $[M+H]^+$: 484.35334 , found 484.3522.

(1S,3aS,3bR,5aS,10aS,10bS,12aS)-10a,12a-dimethyl-1,2,3,3a,3b,4,5,5a,6,7,10,10a,10b,11,12,12a-hexadecahydrocyclopenta[7,8]phenanthro[2,3-d][1,2,3]triazol-1-ol (153f): Dihydrotestosterone (136 mg, 0.47 mmol), ammonium acetate (180 mg, 2.35 mmol), 4-nitrophenyl azide (100 mg, 0.61 mmol), and DMF (1 mL). Reaction time is 12 h. The product was purified by flash column chromatography (CH_2Cl_2 followed by heptane/EtOAc = 4:6) afforded **153f** (142 mg, 96% yield) as an off white semi-solid. m.p. 174 - 175 ˚C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 4.83(s_{br}, 1H), 3.44 (t, *J* = 8.6Hz, 1H), 2.70 – 2.57 (m, 2H), 2.22 – 2.16(m, 2H), 1.88 – 1.76 (m, 2H), 1.67

– 1.47 (m, 5H), 1.39 – 1.30 (m, 4H), 1.23 – 1.13 (m, 2H), 1.04 – 0.97 (m, 1H), 0.93 – 0.85 (m, 3H), 0.67 (s, 3H), 0.65 (s, 3H). **^{13}C NMR** (100 MHz, MeOD) δ 139.8, 138.7, 82.5, 52.1, 49.8, 44.0, 43.2, 38.1, 38.0, 37.9, 37.0, 35.0, 32.2, 30.6, 29.8, 25.2, 24.3, 22.0, 11.9, 11.6. **HRMS** (ESI+): m/z calcd for $C_{19}H_{29}N_3O$ $[M+H]^+$: 316.23832, found 316.2390.

(1R,3aS,3bR,5aS,10aS,10bS,12aR)-10a,12a-dimethyl-1-((R)-6-methylheptan-2-yl)-1,2,3,3a,3b,4,5,5a,6,7,10,10a,10b,11,12,12a-hexadecahydrocyclopenta[7,8]phenanthro[2,3-d][1,2,3]triazole (153g) : Cholestan-3-one (181 mg, 0.47 mmol), ammonium acetate (180 mg, 2.35 mmol), 4-nitrophenyl azide (100 mg, 0.61 mmol), and DMF (1 mL). Reaction time is 12 h. The product was purified by flash column chromatography (CH_2Cl_2 followed by heptane/EtOAc = 4:6) afforded **153g** (169 mg, 88% yield) as an off white solid. m.p. 170 – 171 ˚C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.84 (d, *J* = 15.9 Hz, 1H), 2.74 – 2.69 (m, 1H), 2.37 – 2.29 (m, 2H), 2.07 – 2.02 (m, 1H), 1.86 – 1.80 (m, 1H), 1.75 – 1.71 (m, 1H), 1.63 – 1.57 (m, 3H), 1.54 – 1.47 (m, 2H), 1.39 – 1.32 (m, 4H), 1.27 – 1.22 (m, 4H), 1.16 – 1.09 (m, 5H), 1.06 – 0.98 (m, 3H), 0.95 – 0.91 (m, 4H), 0.87 (d, *J* = 1.7 Hz, 3H), 0.86 (d, *J* = 1.7 Hz, 3H), 0.75 (s, 3H), 0.69 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 142.7, 141.7, 56.5, 56.4, 53.9, 42.6, 42.6, 40.1, 39.7, 37.0, 36.3, 35.9, 35.7, 35.6, 31.8, 29.3, 28.4, 28.1, 25.9, 24.4, 24.0, 23.0, 22.7, 21.4, 18.8, 12.1, 11.8. **HRMS** (ESI+): m/z calcd for $C_{27}H_{45}N_3$ $[M+H]^+$: 412.36860, found 412.3675.

5-chloro-2-(1*H*-1,2,3-triazol-5-yl)phenol (156a): 1-(4-chloro-2-hydroxyphenyl) ethan-1-one (80 mg, 0.47 mmol), ammonium acetate (180 mg, 2.35 mmol), 4-nitrophenyl azide (100 mg, 0.61 mmol), and DMF (1 mL). Reaction time is 24 h. The product was purified by flash column chromatography (CH_2Cl_2 followed by heptane/EtOAc = 6:4) afforded **156a** (71 mg, 77% yield) as an off white solid. m.p. 76 - 77 ˚C. **^{1}H NMR** (300 MHz, DMSO-d_6) δ 8.31 (s, 1H), 7.91 (s, 1H), 7.24 – 7.20 (m, 1H), 6.99 (d, *J* = 8.7 Hz, 1H). **^{13}C NMR** (75 MHz, DMSO-d_6) δ 153.1,

128.4, 126.2, 122.9, 117.8. **HRMS** (ESI+): m/z calcd for $C_8H_6ClN_3O$ $[M+H]^+$: 196.0272, found 196.0268.

5-(3,4-dibromophenyl)-1*H*-1,2,3-triazole (156b): 1-(3,4-dibromophenyl)ethan-1-one (129 mg, 0.47 mmol), ammonium acetate (180 mg, 2.35 mmol), 4-nitrophenyl azide (100 mg, 0.61 mmol), and DMF (1 mL). Reaction time is 24 h. The product was purified by flash column chromatography (CH_2Cl_2 followed by heptane/EtOAc = 6:4) afforded **156b** (112 mg, 80% yield) as an off white solid. m.p. 163 - 164 ˚C. **^{1}H NMR** (300 MHz, DMSO-d_6) δ 8.52 (s, 1H), 8.25 (s, 1H), 7.87 - 7.80 (m, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 134.3, 131.8, 130.2, 126.1, 124.5, 123.0. **HRMS** (ESI+): m/z calcd for $C_8H_5Br_2N_3$ $[M+H]^+$: 301.8924, found 301.8926.

3,8-dihydroindeno[1,2-d][1,2,3]triazole (156c): 1-Indanone (61 mg, 0.47 mmol), ammonium acetate (180 mg, 2.35 mmol), 4-nitrophenyl azide (100 mg, 0.61 mmol), and DMF (1 mL). Reaction time is 12 h. The product was purified by flash column chromatography (CH_2Cl_2 followed by heptane/EtOAc = 4:6) afforded **156c** (55 mg, 75% yield) as an off white semi-solid. m.p. 121 – 122 ˚C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.72 (d, *J* = 7.4 Hz, 1H), 7.60 (d, *J* = 7.4 Hz, 1H), 7.42 – 7.32 (m, 2H), 3.81(s, 2H). **^{13}C NMR** (75 MHz, DMSO-d_6) δ 154.0, 148.2, 133.0, 128.4, 127.3, 121.5, 28.6. **HRMS** (ESI+): m/z calcd for $C_9H_7N_3$ $[M+H]^+$: 158.07127, found 158.0697.

(6bS,8aS,12aS,12bR)-8a-methyl-1,2,6b,7,8,8a,9,12,12a,12b-decahydronaphtho[2',1':4,5]indeno[1,2-d][1,2,3]triazol-4-ol (**156d**): Estrone (127 mg, 0.47 mmol), ammonium acetate (180 mg, 2.35 mmol), 4-nitrophenyl azide (100 mg, 0.61 mmol), and DMF (1 mL). Reaction time is 48 h. The product was purified by flash column chromatography (CH_2Cl_2 followed by heptane/EtOAc = 4:6) afforded **156c** (112 mg, 81**%** yield) as an off white semi-solid. m.p. 264 – 265 ˚C.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.06 (d, *J* = 8.5 Hz, 1H), 6.54 – 6.52 (m, 1H), 6.47 (1H, *J* = 2.4 Hz, 1H), 2.86 – 2.67 (m, 3H), 2.45 – 2.26 (m, 3H), 2.19 – 2.09 (m, 2H), 1.92 – 1.88 (m, 1H), 1.81 – 1.71 (m, 1H), 1.69 – 1.63 (m, 1H), 1.59 – 1.49 (m, 1H), 1.47 – 1.35 (m, 1H), 1.26 – 1.16 (m, 1H), 0.94 (s, 3H). **^{13}C NMR** (100 MHz, MeOD) δ 161.3, 156.0, 151.2, 137.0, 130.1, 125.8, 115.0, 112.8, 60.7, 43.8, 39.2, 37.1, 33.8, 29.0, 27.0, 25.7, 23.1, 18.3. **HRMS** (ESI+): m/z calcd for $C_{18\ h21}N_3O$ $[M+H]^+$: 296.17572, found 296.1757.

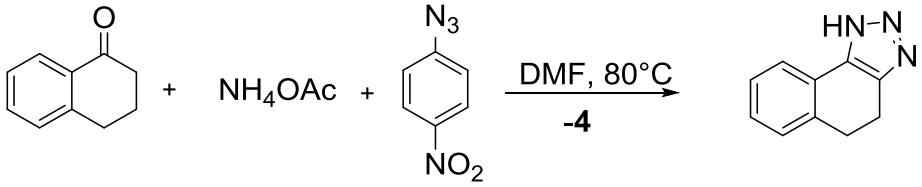
(3S,8S,9S,10R,13S,14S,17S)-17-((S)-4,5-dihydro-1H-1,2,3-triazol-5-yl)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-ol (156e): Pregnenolone (148 mg, 0.47 mmol), ammonium acetate (180 mg, 2.35 mmol), 4-nitrophenyl azide (100 mg, 0.61 mmol), and DMF (1 mL). Reaction time is 24 h. The product was purified by flash column chromatography (CH_2Cl_2 followed by heptane/EtOAc = 4:6) afforded **156e** (110 mg, 69% yield) as an off white semi-solid. m.p. 237-238 ˚C. **^{1}H NMR** (300 MHz, DMSO – d_6 + TFA, 1 drop) δ 7.85 (s, 1H), 5.31 (s, 1H), 3.32 – 3.23 (m, 1H), 2.82 – 2.75 (m, 1H), 2.20 – 1.92 (m, 4H), 1.77 – 1.55 (m, 5H), 1.45 – 1.18 (m, 7H), 1.03 – 0.86 (m, 6H), 0.49 – 0.43 (m, 3H). **^{13}C NMR** (100 MHz, MeOD) δ 142.3, 142.2, 122.3, 72.4, 57.3, 51.8, 51.4, 44.9, 43.0, 38.6, 37.8, 33.7, 33.3, 33.0, 32.3, 27.7, 25.5, 22.0, 19.9, 13.5. **HRMS** (ESI+): m/z calcd for $C_{21}H_{31}N_3O$ $[M+H]^+$: 342.25397, found 342.2545.

2-(1H-1,2,3-triazol-5-yl)pyridine (156f): 2-Acetopyridine (57 mg, 0.47 mmol), ammonium acetate (180 mg, 2.35 mmol), 4-nitrophenyl azide (100 mg, 0.61 mmol), and DMF (1 mL). Reaction time is 12 h. The product was purified by flash column chromatography (CH_2Cl_2 followed by heptane/EtOAc = 4:6) afforded **156f** (61 mg, 89% yield) as an off white solid. m.p. 142 - 143 ˚C. **^{1}H NMR** (300 MHz, MeOD) δ 8.58 (d, *J* = 8 Hz, 1H), 8.30 (s, 1H), 8.03 (d, *J* = 8 Hz, 1H), 7.93 – 7.87 (m, 1H),

7.93 – 7.34 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.7, 137.4, 126.1, 124.7, 123.5, 121.1. **HRMS** (ESI+): m/z calcd for $C_7H_6N_4$ $[M+H]^+$: 147.06651, found 147.0663.

2,6-di(1*H*-1,2,3-triazol-5-yl)pyridine (156g): 2,6-Diacetylpyridine (77 mg, 0.47 mmol), ammonium acetate (360 mg, 4.70 mmol), 4-nitrophenyl azide (200 mg, 1.22 mmol), and DMF (1 mL). Reaction time is 48 h. The product was purified by flash column chromatography (CH_2Cl_2 followed by heptane/EtOAc = 4:6) afforded **12g** (70 mg, 70% yield) as an off white semi-solid. m.p. 158 - 159 ˚C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.53 (s, 2H), 8.03 - 7.94 (m, 3H). **^{13}C NMR** (75 MHz, DMSO-d6) δ 149.6, 145.7, 138.9, 128.6, 119.6. **HRMS** (ESI+): m/z calcd for $C_9H_7N_7$ $[M+H]^+$: 214.0835, found 214.0838. Spectroscopic data for **156g** are consistent with previously reported data for the compound.[9]

3.4.3 Bulk synthesis of *NH*-1,2,3-triazole 148a



146a (2 g) (5.2 g) **131a** (2.9 g) **148a** (1.92 g, 82%)

To a 100 mL round-bottom flask equipped with a magnetic stir bar was added an equivalent of **146a** (2 g, 13.7 mmol), ammonium acetate (5.2 g, 68.5 mmol), **131a** (2.9 g, 17.7 mmol). The mixture was dissolved in anhydrous DMF (20 mL) and stirred at 80 °C for 12 hr. Upon completion, the solvent was evaporated off and the resulting reaction mixture was diluted with ethyl acetate (3x 200 mL), washed with water, dried over $MgSO_4$ and evaporated under reduced pressure. The residue was further purified by column chromatography (silica gel), at first with CH_2Cl_2 as eluent to remove of all 4-nitroaniline formed during

the reaction followed by using a mixture of heptane/EtOAc = 5:2 as eluent to afford **148a** (1.92 g, 82%) as an off-white solid.

3.5 Notes and references

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Chapter 4

A one-pot procedure for the synthesis of “click-ready” triazoles from ketones

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Sampad Jana carried out the experiments, analyzed the data and wrote the manuscript.

4.1 Introduction

The propargyl group is a key functional group which is widely used in forefront research for various applications in organic, medicinal, and material chemistry.[1a-f] For instance, propargyl derivatives have been used as essential starting materials to synthesize various heterocyclic moieties such as triazole, indole, imidazole, and pyrazoline *via* C-C, or C-X (X= O and N) bond formation reactions.[1a-f] Propargyl moieties are also used as starting points in various metathesis and oligomerization reactions.[2b] In medicinal chemistry, this group has been found to be a key functionality in various biologically active molecules. Of the compounds shown in figure 8, Rasagiline **a** and slegiline **b** are monoamine oxidase inhibitors and also they are known as commercial drugs for Parkinson disease,[2c] the showdomycin probe **c** is attached to a fluorophore to identify diverse enzymes,[2d] the duocarmycin derivative **d** exhibits antitumor activity,[2e] and arylsulfonyl-*NH*-1,2,3-triazole **e** is a VIM-2 β-lactamase inhibitor (Figure 8).[2g] Moreover, propargyl group functionalized drug molecules are widely used as bioorthogonal tags for detecting drug like activities in cells by spontaneous Raman spectroscopic techniques.[2h]

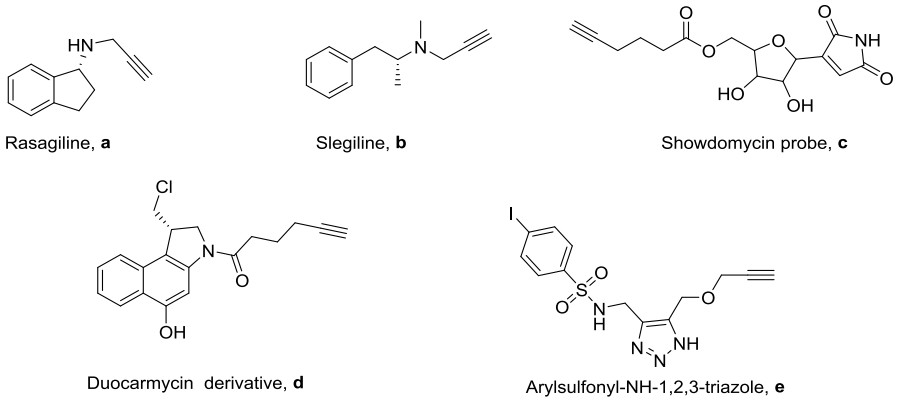
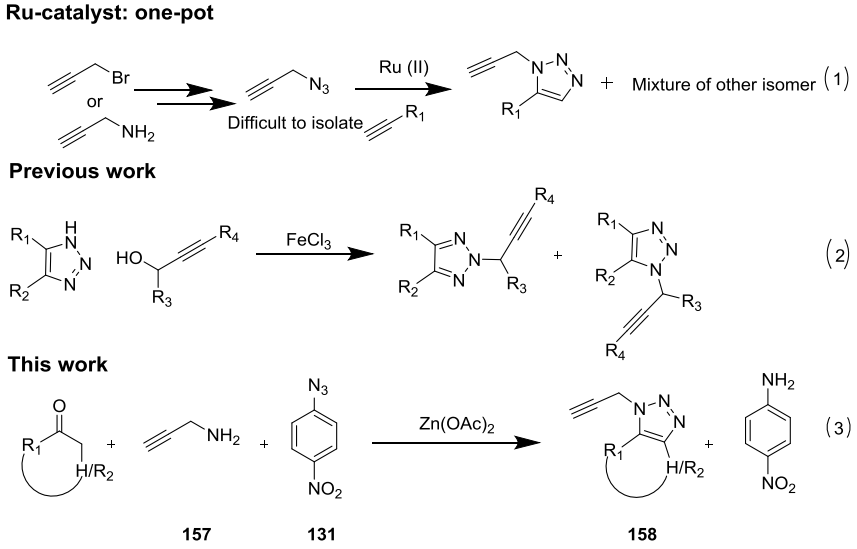


Figure 8 Illustration of pharmaceutically active propargyl moieties.

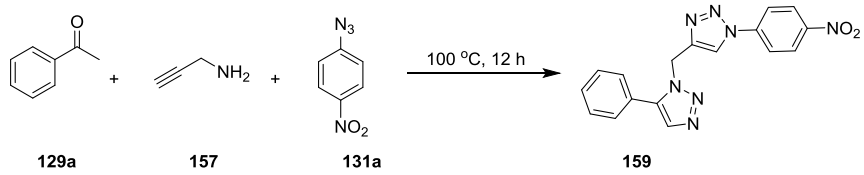
1,2,3-Triazoles are of great importance in organic synthesis due to their higher stability towards biodegradationin comparison to their

isosteres such as amide bonds.[2a] Cu(I)- and Ru(II)-catalyzed regioselective azide alkyne cycloaddition reactions are widely used to synthesize 1,4- and 1,5-disubstituted 1,2,3-triazoles, respectively.[4] Considering the importance of the triazole moieties several analogous methodologies have been discovered.[4,5] Interestingly, the *N*-substituted propargyl triazoles are scarcely reported. This could be due to the instability of propargyl azide even at room temperature.[6] However, in 2010 Shi and co-workers have reported an iron(III)-catalyzed procedure for the preparation of propargyl substituted triazoles starting from *NH*-triazoles and propargyl alcohols (scheme 31, equation 2).[7] Unfortunately, the scope of this reaction is limited due to the lack of regioselectivity. Consequently, a cost effective and a general methodology from readily available building blocks is desired to functionalize triazole heterocycles with propargyl functionalities. Such compounds would be very useful to click a second moiety to the triazole.



Scheme 31. Three distinct approaches to *N*-substituted propargyl 1,2,3-triazole

Very recently, we have developed a potent triazolization strategy towards the synthesis of 1,5–disubstituted or fused 1,2,3-triazole form commercially available ketones and amines.[3] Our initial attempts to synthesize the propargyl substituted triazole by this method resulted in a complicated reaction mixture which could be due to elevated temperature (100 °C) used in this reaction. A careful analysis and separation of this crude reaction mixture resulted in the isolation of 15% of the bis-triazole derivative **159**, which was derived from the thermal cycloaddition reaction of 4-nitrophenyl azide **131a** with the propargyl group before or after the triazolization reaction (Scheme 32). However, from the mechanistic study of our previous triazolization reaction, it was evident that enamine formation was the rate determining step which usually requires 100 °C to proceed at a workable speed. Thus, we assumed that the presence of Lewis acid catalyst could increase the reaction rate by activating the keto group at comparatively lower temperature and the subsequent triazolization reaction could also proceed under these relative mild conditions.



129a 157 131a 159

Scheme 32 Formation of undesired bis-triazole.

4.2 Results and discussions

In order to prove this hypothesis, we initiated our studies with cyclohexanone (1 equiv.), propargyl amine (2 equiv.), and 4-nitrophenyl azide (1.4 equiv.) as standard substrates. Interestingly, initial screening of 10 mol% $Sc(OTf)_3$ in CH_2Cl_2 at 40 °C afforded the triazolization product up to 39% yield after 24 h (entry 1, Table 1). Inspired by this result, several Lewis acid catalysts such as $Fe(OTf)_3$, $Zn(OTf)_2$, $BF_3.OEt_2$, and $Zn(OAc)_2$ were screened in our model reactions (entry 2-5, Table 8). Among these. $Zn(OAc)_2$ showed the best catalytic

activity which gave the expected product in 54% of isolated yield (entry 5, Table 8). A gradual increase in the yield was observed when the amount of $Zn(OAc)_2$ was increased from 10 to 100 mol% (entry 5-7, Table 8).

Entry	catalyst (mol%)	temp (°C)	solvent	Time (h)	Yield[b] (%)
1	$Sc(OTf)_3$ (10 mol%)	40	DCM	24	39
2	$Fe(OTf)_3$ (10 mol%)	40	DCM	24	43
3	$Zn(OTf)_2$ (10 mol%)	40	DCM	24	52
4	$BF_3.OEt_2$ (10 mol%)	40	DCM	24	32
5	$Zn(OAc)_2$ (10 mol%)	40	DCM	24	54
6	$Zn(OAc)_2$ (50 mol%)	40	DCM	24	62
7	$Zn(OAc)_2$ (100 mol%)	40	DCM	24	67
8	$Zn(OAc)_2$ (100 mol%)	40	DMF	24	66
9	**$Zn(OAc)_2$ (100 mol%)**	**60**	**DMF**	**10**	**75**
10	$Zn(OAc)_2$ (100 mol%)	70	DMF	6	61
11	$Zn(OAc)_2$ (100 mol%)	60	Ethanol	10	28
12	$Zn(OAc)_2$ (100 mol%)	60	THF	10	62
13	$Zn(OAc)_2$ (100 mol%)	60	DMSO	10	51
14	$Zn(OAc)_2$(100 mol%)	60	EtOH	10	13
15	no	60	DMF	10	23

Table 8 Optimization of reactions conditions[a]

[a]Standard reaction condition: 1 equiv. of cyclohexanone **129**, 2 equiv. of propargyl amine **157**, 1.4 equivalent of 4- nitrophenyl azide 1**31a**, 40 mg of 4Å MS and 1 equiv. $Zn(OAc)_2$ were mixed in 0.2 mL solution of DMF at 60 °C. [b]Isolated yield.

Interestingly, a slight improvement in the yield was observed when we replaced CH_2Cl_2 with DMF (entry 8, Table 8). Further investigation showed that this reaction is highly temperature dependent, increasing temperature from 40 to 60 ˚C in DMF resulted in 75% yield after 10 h (entry 9, Table 8) whereas an increase in temperature from 60 to 70 ˚C resulted in diminished yield (61%, entry 10, Table 8). Among the tested solvents, DMF and CH_2Cl_2 gave best result whereas DMSO, THF and ACN gave moderate yield and protic solvent such as EtOH afforded

lower yield. As expected, a small amount of desired product was obtained while performing the reaction without any Lewis acid catalyst (entry 15, Table 8). We found that cyclohexanone, propargyl amine, and 4-nitrophenyl azide **3** in a respective molar ratio of 1:2:1.4 using 1 equiv. of $Zn(OAc)_2$ in a 2.5 molar solution of DMF over a period of 10 h at 60 °C afforded **5** in 75% yield.

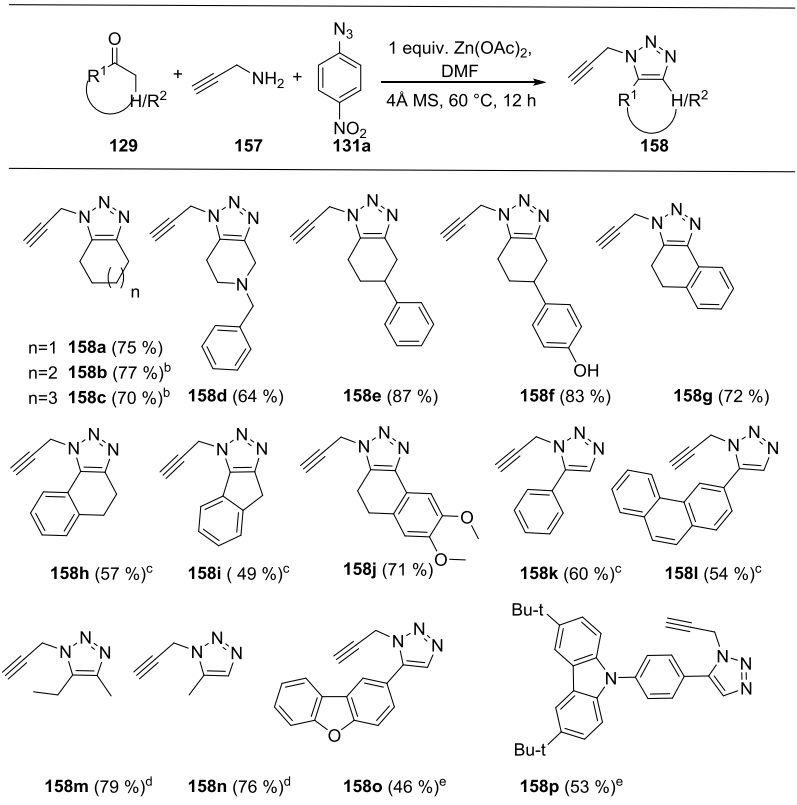


Table 9 Substrate scope with respect to a variety of ketones[a]

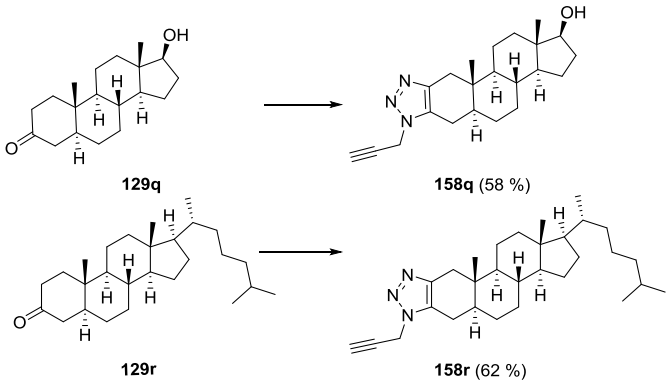
[a]reaction conditions: **135** (1 equiv.), **164** (2 equiv.), 1**37a** (1.4 equiv.), $Zn(OAc)_2$ (1 equiv.), DMF (0.4 mL), 60 °C, 10 h, Isolated yields. [b]8 h, [c]24 h. [d]40 °C, 24 h. [e]36 h.

With these optimized conditions in hand, the scope of this triazolization reactions was investigated. An array of cyclic ketones were employed in the optimized reaction condition which afforded the

propargyl functionalized triazole derivatives **158a – 158f** in good yields regardless of the size of cyclic ketones (Table 9). Similarly, screening of different aromatic bicyclic ketones also leads to the corresponding products **158g – 158j** in excellent yield (Table 9). It is worth mentioning that high regioselectivity was observed for the product **158g** derived from 2-tetralone (Table 9). Evidently, the product formation occurs through the cycloaddition of azide with the more stable enamine conjugated to the aromatic ring.

Next, we investigated the scope of the reaction with respect to acetyl substituted aromatic hydrocarbons such as acetophenone and 3-acetyl phenanthrene which delivered moderate yields of the expected products under the optimized reaction circumstances (**158k** & **158l**) (Table 9). The extension of this protocol to symmetrical acyclic ketones resulted in the formation of 1,4,5-trisubstituted 1,2,3-triazoles in good yield (**158m** & **158n**) (Table 9). The utility of this reaction is further proved in heterocycles of interest in material research such as dibenzofuran and carbazole. Thus, this triazolization strategy decorated these useful heterocycles with propargyl groups (**158o** & **158p**) (Table 9) in good yield even though these reactions required longer reaction time than the previously optimized conditions.

Modification of natural products such as alkaloids, nucleosides, and steroids with propargyl groups for various applications such as Cu(I) triggered immobilization are of common interest in the area of medicinal chemistry.[2a] By taking into account the fact that enolizable ketones are abundantly available in various natural products, this protocol provides an easy pathway for the functionalization of natural products with a 'clickable' propargyl group. The application of this methodology to dihydrotestosterone **129q**, an androgen hormone, led to highly regioselective 2,3-A ring fused triazole **158q** in good yield. In a similar manner, cholesterol-derived cholestan-3-one **129r** under this reaction circumstances afforded the A-ring fused triazole **158r** in good yield (Scheme 33).



Scheme 33 Substrate scope with respect to the natural products

Thus, in order to prove the usefulness of these propargyl substituted triazoles, a series of bis-triazole derivatives **160a** – **160g** (Table 10) have been prepared via CuAAc click reaction. Although there are several reports on C-C and N-N linked bis-triazoles formation, a suitable methodology for formation of N-C linked unsymmetrical bis-triazoles was still lacking.[8] Here we report for the first time a N-C linked bis-triazole hybrid of porphyrin and carbazole **160a** (entry 1). Barthélémy *et al.* reported that the uptake of oligonucleotide increased manyfold across the cell membrane when it is attached with lipophilic cholesterol with triazole linkage.[9] As a possible alternative to this previously reported synthetic strategy, we also developed a bis-triazole linked compound **160b** derived from azidothymidine (AZT) **159b** and propargyl derived cholestan-3-one **158r** in a straightforward manner (entry 2). The amphiphilic cholesterol derivative **160c** has been prepared in good yield from cholesterol **158r** and tri-ethylene glycol azide **159c** (entry 3).[10] The propargyl substituted steroid **158q** was further functionalized with azido sugar **159d**, leading to a new type of bis-triazole hybrid system **160d** in excellent yield (entry 4). The sugar azide 1**59e** also coupled with propargyl triazole **158k** to give **160e** in excellent yield (entry 5).

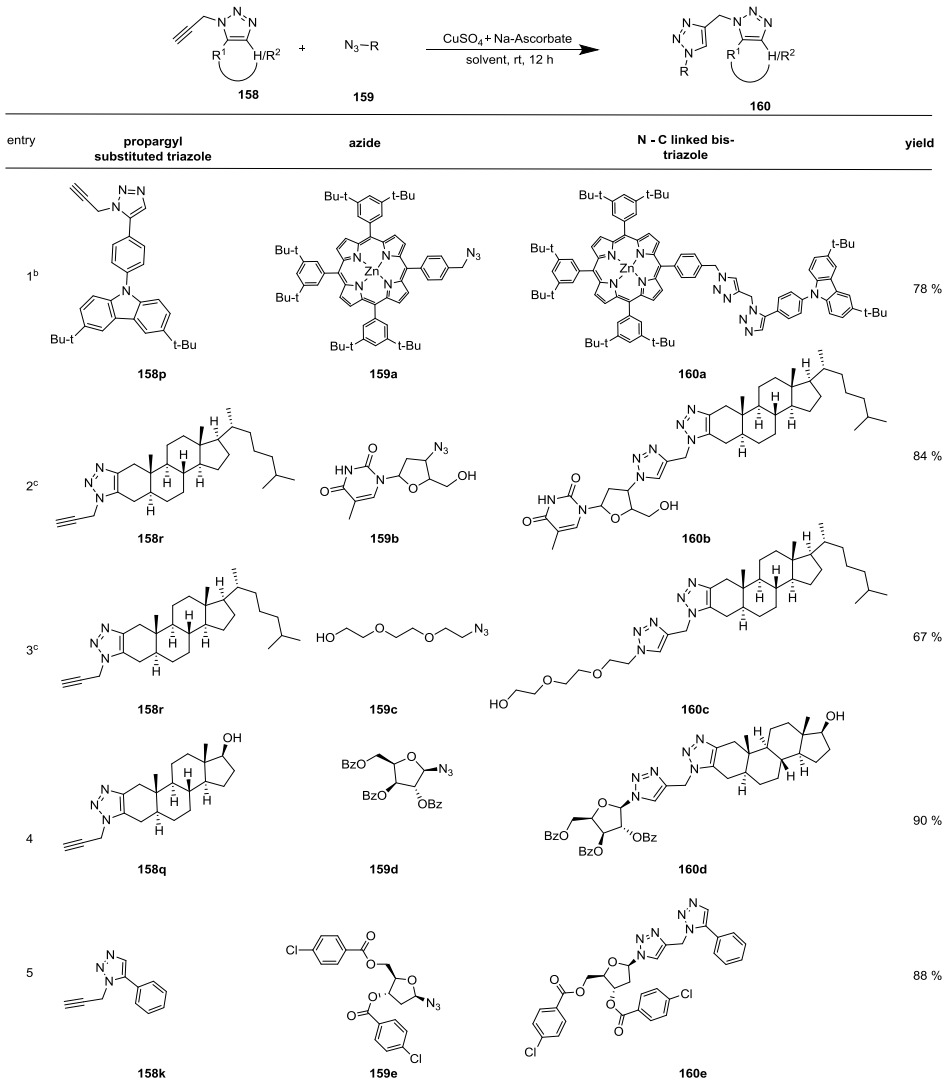
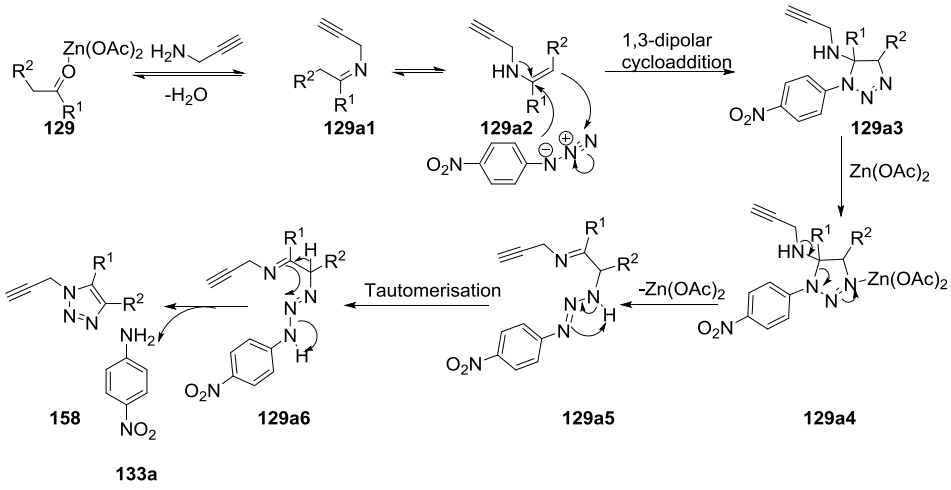


Table 10 Synthesis of N-C linked unsymmetrical bis-triazole derivatives:[a]

[a]**158** (1 equiv.), **159** (1.2 equiv.), $CuSO_4$ (0.05 equiv.), Na-Ascorbate (0.11 equiv.), rt, 12 h, isolated yield. [b]t-BuOH/H_2O/DCM (1:1:1), 6 h. [c]t-BuOH/H_2O/THF (1:1:1), 36 h

On the basis of previously reported work, here we have proposed a plausible mechanism for this reaction (Scheme 34). Initially, enamine is formed from propargyl amine and enolizable ketone in a Lewis acid

mediated reaction. Then the enamine undergoes cycloaddition with azide to form a triazoline intermediate. Subsequently, the triazoline intermediate leads to the desired product via ring opening and ring closing intermediates with the elimination of a molecule of 4–nitrophenyl aniline.



Scheme 34 Proposed mechanism for the formation of propargyl triazole

4.3 Conclusion

In conclusion, we have developed a highly efficient and regiospecific $Zn(OAc)_2$ mediated synthesis of propargyl functionalized triazole derivatives in a single step from ketones and propargyl amine. Subsequently, Cu(I) reactions of these propargyl triazoles with various organic azides having supramolecular and medicinal interest lead to novel N-C linked bis-triazole moieties in a regioselective manner with excellent yield. This newly developed method has the following advantages: (1) it gives access in a single step to propargyl triazoles, which is not possible by any other reported methods (2) it uses cheap and readily available building blocks, (3) it can be extended to natural products containing enolizable ketone groups. Considering the

importance of these products we believe that this methodology could draw attention for various applications in the field of medicinal and material chemistry. Further studies of these propargyl triazole analogues for medicinal chemistry applications as well as for metal ligand binding studies are under investigation and will be reported in due course.

4.4 Experimental Section

4.4.1 Experimental procedure

4.4.1.1 General procedure for the preparation of propargyl substituted 1,2,3-triazoles

To an oven-dried screw-capped reaction tube equipped with a magnetic stirring bar was added the ketone, propargyl amine, 4-nitrophenyl azide, $Zn(OAc)_2$ and 4 Å molecular sieves. The mixture was dissolved in DMF (0.4 mL) and stirred at 60 °C for 10-36 hour. Upon completion, the solvent was removed in *vacuo*. The crude reaction mixture was then directly purified by column chromatography (silica gel) at first with CH_2Cl_2 as eluent to remove all 4-nitroaniline formed during the reaction followed by using a mixture of heptane and ethyl acetate as eluent to afford the corresponding propargyl substituted 1,2,3-triazoles as off-white solids or semi-solids.

4.4.2 Charactarization data

1-(Prop-2-yn-1-yl)-4,5,6,7-tetrahydro-1*H*-benzo[d][1,2,3]triazole(158a): cyclohexanone (100 mg, 1.01 mmol), propargyl amine (112 mg, 2.03 mmol), 4-nitrophenyl azide (234 mg, 1.42 mmol), zinc acetate (187 mg, 1.01 mmol), 4 Å molecular sieves (40 mg) and DMF (0.4 mL). Reaction time was 10 h. The product was purified by flash column chromatography (CH_2Cl_2 followed by heptane/EtOAc = 3:2) affording **158a** (123 mg, 75% yield) as an off white semi-solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.05 (t, *J* = 2.1 Hz, 2H), 2.73 (dd, *J* = 13.3, 6.8 Hz, 4H), 2.45 (t, *J* = 2.6 Hz, 1H), 1.90 – 1.77 (m,

4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.1, 132.23, 75.6, 74.6, 37.6, 22.6, 22.4, 21.9, 20.1. HRMS (ESI+): m/z calcd for $C_9H_{11}N_3$ $[M+H]^+$: 162.1025, found 162.1034.

1-(Prop-2-yn-1-yl)-1,4,5,6,7,8-hexahydrocyclohepta[d][1,2,3]triazole(158b): cycloheptanone (100 mg, 0.89 mmol), propargyl amine (98 mg, 1.78 mmol), 4-nitrophenyl azide (204 mg, 1.24 mmol), zinc acetate (164 mg, 0.89 mmol), 4 Å molecular sieves (40 mg) and DMF (0.4 mL). Reaction time is 8 h. The product was purified by flash column chromatography (CH_2Cl_2 followed by heptane/EtOAc = 3:2) affording **158b** (125 mg, 77% yield) as an off white semi-solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.06 (d, *J* = 2.6 Hz, 2H), 2.92 – 2.78 (m, 4H), 2.43 (t, *J* = 2.6 Hz, 1H), 1.91 – 1.81 (m, 2H), 1.80 – 1.68 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.8, 135.1, 76.01, 74.4, 37.9, 30.8, 27.3, 27.2, 26.8, 24.2. HRMS (ESI+): m/z calcd for $C_{10}H_{13}N_3$ $[M+H]^+$: 176.1182, found 176.1193.

1-(Prop-2-yn-1-yl)-4,5,6,7,8,9-hexahydro-1*H*-cycloocta[d][1,2,3]triazole(158c): cyclooctanone (100 mg, 0.78 mmol), propargyl amine (87 mg, 1.58 mmol), 4-nitrophenyl azide (179 mg, 1.09 mmol), zinc acetate (145 mg, 0.79 mmol), 4 Å molecular sieves (40 mg) and DMF (0.4 mL). Reaction time is 8 h. The product was purified by flash column chromatography (CH_2Cl_2 followed by heptane/EtOAc = 3:2) affording **158c** (105 mg, 70% yield) as an off white semi-solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.06 (d, *J* = 2.6 Hz, 2H), 2.95 – 2.83 (m, 4H), 2.45 (t, *J* = 2.6 Hz, 1H), 1.92 – 1.84 (m, 2H), 1.80 – 1.71 (m, 2H), 1.59 – 1.41 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.2, 133.4, 76.1, 74.5, 37.7, 28.1, 26.0, 25.9, 24.7, 24.5, 21.7. HRMS (ESI+): m/z calcd for $C_{11}H_{15}N_3$ $[M+H]^+$: 190.1338 , found 190.1336.

5-Benzyl-1-(prop-2-yn-1-yl)-4,5,6,7-tetrahydro-1*H*-[1,2,3]triazolo[4,5-c]pyridine(158d): 1-benzylpiperidin-4-one (100 mg, 0.52 mmol), propargyl amine (58.2 mg, 1.05 mmol), 4-nitrophenyl azide (121 mg, 0.73 mmol), zinc acetate (97 mg, 0.52 mmol), 4 Å molecular sieves (40 mg) and DMF (0.4 mL). Reaction time is 10 h. The

product was purified by flash column chromatography (CH_2Cl_2 followed by heptane/EtOAc = 3:2) affording **158d** (85 mg, 64% yield) as an off white semi-solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 – 7.26 (m, 5H), 5.07 (d, *J* = 2.6 Hz, 2H), 3.76 (s, 2H), 3.69 (s, 2H), 2.83 (s, 4H), 2.46 (t, *J* = 2.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.1, 138.0, 131.0, 129.1, 128.5, 127.5, 75.3, 75.0, 61.8, 49.8, 49.2, 37.9, 21.0. HRMS (ESI+): m/z calcd for $C_{15}H_{16}N_4$ $[M+H]^+$: 253.1447 , found 253.1451.

5-Phenyl-1-(prop-2-yn-1-yl)-4,5,6,7-tetrahydro-1*H*-benzo[d][1,2,3]triazole (158e): 4-phenylcyclohexan-1-one (100 mg, 0.57 mmol), propargyl amine (63.2 mg, 1.14 mmol), 4-nitrophenyl azide (132 mg, 0.80 mmol), zinc acetate (105 mg, 0.57 mmol), 4 Å molecular sieves (40 mg) and DMF (0.4 mL). Reaction time is 10 h. The product was purified by flash column chromatography (CH_2Cl_2 followed by heptane/EtOAc = 3:2) affording **158e** (118 mg, 87% yield) as an off white semi-solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.32 (m, 2H), 7.27 – 7.23 (m, 3H), 5.1 – 5.0 (m, 2H), 3.13 (dd, *J* = 15.4, 4.9 Hz, 1H), 3.06 – 2.96 (m, 1H), 2.93 – 2.76 (m, 3H), 2.47 (t, *J* = 2.6 Hz, 1H), 2.26 – 2.17 (m, 1H), 2.09 – 1.96 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.93, 144.35, 132.04, 128.76, 126.98, 126.75, 75.50, 74.84, 40.61, 37.86, 30.03, 29.73, 20.12. HRMS (ESI+): m/z calcd for $C_{15}H_{15}N_3$ [M+H]+: 238.1338, found 238.1338.

4-(1-(Prop-2-yn-1-yl)-4,5,6,7-tetrahydro-1*H*-benzo[d][1,2,3]triazol-5-yl)phenol (158f): 4-(4-hydroxyphenyl)cyclohexan-1-one (100 mg, 0.52 mmol), propargyl amine (87.9 mg, 1.05 mmol), 4-nitrophenyl azide (121 mg, 0.73 mmol), zinc acetate (96 mg, 0.52 mmol), 4 Å molecular sieves (40 mg) and DMF (0.4 mL). Reaction time is 10 h. The product was purified by flash column chromatography (CH_2Cl_2 followed by heptane/EtOAc = 3:2) affording **158f** (110 mg, 83% yield) as an off white solid. m.p. 186 – 187 ˚C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.21 (s, 1H), 7.11 (d, *J* = 8.5 Hz, 2H), 6.71 (d, *J* = 8.5 Hz, 2H), 5.24 (d, *J* = 2.5 Hz, 2H), 3.55 (t, *J* = 2.6 Hz, 1H), 2.90 – 2.80 (m, 3H), 2.78 – 2.60 (m, 2H), 2.08 – 1.79 (m, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 155.75, 143.17, 135.49, 132.04, 127.75, 115.13, 77.05, 76.69, 36.99, 29.76, 29.41,

19.29. HRMS (ESI+): m/z calcd for $C_{15}H_{15}N_3O_1$ $[M+H]^+$: 254.1287, found 254.1291.

3-(Prop-2-yn-1-yl)-4,5-dihydro-3*H*-naphtho[1,2-d][1,2,3]triazole (158g): 3,4-dihydronaphthalen-2(1*H*)-one (100 mg, 0.68 mmol), propargyl amine (75 mg, 1.36 mmol), 4-nitrophenyl azide (157 mg, 0.95 mmol), zinc acetate (126 mg, 0.68 mmol), 4 Å molecular sieves (40 mg) and DMF (0.4 mL). Reaction time is 10 h. The product was purified by flash column chromatography (CH_2Cl_2 followed by heptane/EtOAc = 3:2) affording **158g** (103 mg, 72% yield) as an off white solid. m.p. 86.5 – 87.5 ˚C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (d, *J* = 7.4 Hz, 1H), 7.34 – 7.27 (m, 1H), 7.25 – 7.18 (m, 2H), 5.15 (d, *J* = 2.6 Hz, 2H), 3.21 – 2.94 (m, 4H), 2.48 (t, *J* = 2.6 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.2, 133.5, 132.9, 128.5, 128.3, 127.7, 127.4, 122.1, 75.3, 75.1, 38.0, 28.5, 19.1. HRMS (ESI+): m/z calcd for $C_{13}H_{11}N_3$ $[M+H]^+$: 210.1025, found 210.1026.

1-(Prop-2-yn-1-yl)-4,5-dihydro-1*H*-naphtho[1,2-d][1,2,3]triazole (158h): 3,4-dihydronaphthalen-1(2*H*)-one (100 mg, 0.68 mmol), propargyl amine (75 mg, 1.36 mmol), 4-nitrophenyl azide (157 mg, 0.95 mmol), zinc acetate (126 mg, 0.68 mmol), 4 Å molecular sieves (40 mg) and DMF (0.4 mL). Reaction time is 10 h. The product was purified by flash column chromatography (CH_2Cl_2 followed by heptane/EtOAc = 3:2) affording **158h** (82 mg, 57% yield) as an off white semi-solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.4 Hz, 1H), 7.38 - 7.28 (m, 3H), 5.38 (d, *J* = 2.2 Hz, 2H), 3.12 – 2.89 (m, 4H), 2.51 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.7, 137.3, 131.5, 129.3, 128.9, 127.4, 124.8, 123.1, 76.1, 75.6, 39.7, 30.3, 20.8. HRMS (ESI+): m/z calcd for $C_{13}H_{11}N_3$ $[M+H]^+$: 210.1025, found 210.1029.

3-(Prop-2-yn-1-yl)-3,8-dihydroindeno[1,2-d][1,2,3]triazole (158i): 2,3-dihydro-1*H*-inden-1-one (100 mg, 0.75 mmol), propargyl amine (83 mg, 1.51 mmol), 4-nitrophenyl azide (173 mg, 1.05 mmol), zinc acetate (139 mg, 0.75 mmol), 4 Å molecular sieves (40 mg) and DMF (0.4 mL). Reaction time is 10 h. The product was purified by flash column chromatography (CH_2Cl_2 followed by heptane/EtOAc = 3:2)

affording **158i** (72 mg, 49% yield) as an off white semi-solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 – 7.75 (m, 1H), 7.56 (dd, *J* = 6.6, 0.8 Hz, 1H), 7.41 (td, *J* = 7.3, 3.9 Hz, 1H), 7.35 (td, *J* = 7.5, 1.4 Hz, 1H), 5.37 (d, *J* = 2.6 Hz, 2H), 3.77 (s, 2H), 2.56 (t, *J* = 2.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.0, 147.7, 141.5, 129.5, 127. 6, 127.4, 126.7, 121.0, 75.6, 75.5, 39.2, 29.2. HRMS (ESI+): m/z calcd for $C_{12}H_9N_3$ $[M+H]^+$: 196.0869, found 196.0874.

7,8-Dimethoxy-3-(prop-2-yn-1-yl)-4,5-dihydro-3*H*-naphtho[1,2-d][1,2,3]triazole (158j): 6,7-dimethoxy-3,4-dihydronaphthalen-1(2*H*)-one (100 mg, 0.48 mmol), propargyl amine (53.4 mg, 0.97 mmol), 4-nitrophenyl azide (111 mg, 0.67 mmol), zinc acetate (89 mg, 0.48 mmol), 4 Å molecular sieves (40 mg) and DMF (0.4 mL). Reaction time is 10 h. The product was purified by flash column chromatography (CH_2Cl_2 followed by heptane/EtOAc = 3:2) affording **158j** (92 mg, 71% yield) as an off white solid. m.p. 147 – 148 ˚C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (s, 1H), 6.77 (s, 1H), 5.15 (d, *J* = 2.6 Hz, 2H), 3.95 (s, 3H), 3.89 (s, 3H), 3.04 (s, 4H), 2.49 (t, *J* = 2.6 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.4, 148.4, 144.3, 131.9, 125.8, 121.2, 111.8, 105.6, 75.3, 75.1, 56.2, 56.1, 38.01, 28.1, 19.3. HRMS (ESI+): m/z calcd for $C_{15}H_{15}N_3O_2$ $[M+H]^+$: 270.1236, found 270.1242.

5-Phenyl-1-(prop-2-yn-1-yl)-1*H*-1,2,3-triazole (158k): acetophenone (100 mg, 0.83 mmol), propargyl amine (92 mg, 1.66 mmol), 4-nitrophenyl azide (191 mg, 1.16 mmol), Zinc acetate (153 mg, 0.83 mmol), 4 Å molecular sieves (40 mg) and DMF (0.4 mL). Reaction time is 24 h. The product was purified by flash column chromatography (CH_2Cl_2 followed by heptane/EtOAc = 3:2) affording **158k** (91 mg, 60% yield) as an off white semi-solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.63 – 7.47 (m, 5H), 5.13 (d, *J* = 2.6 Hz, 2H), 2.48 (t, *J* = 2.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.1, 133.1, 129.9, 129.3, 129.0, 128.8, 126.5, 76.6, 74.9, 38.3. HRMS (ESI+): m/z calcd for $C_{11}H_9N_3$ $[M+H]^+$: 184.0869, found 184.0869.

5-(Phenanthren-3-yl)-1-(prop-2-yn-1-yl)-1*H*-1,2,3-triazole(158l): 1-(phenanthren-3-yl)ethan-1-one (100 mg, 0.45 mmol), propargyl amine

(50 mg, 0.90 mmol), 4-nitrophenyl azide (104 mg, 0.63 mmol), zinc acetate (83 mg, 0.45 mmol), 4 Å molecular sieves (40 mg) and DMF (0.4 mL). Reaction time is 24 h. The product was purified by flash column chromatography (CH_2Cl_2 followed by heptane/EtOAc = 3:2) affording **158l** (70 mg, 54% yield) as an off white solid. m.p. 126 – 127 ˚C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.81 (d, *J* = 8.7 Hz, 1H), 8.72 (d, *J* = 8.0 Hz, 1H), 8.08 (d, *J* = 1.8 Hz, 1H), 7.94 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.89 (s, 1H), 7.85 (d, *J* = 8.9 Hz, 1H), 7.81 – 7.76 (m, 2H), 7.75 – 7.64 (m, 2H), 5.22 (d, *J* = 2.6 Hz, 2H), 2.51 (t, *J* = 2.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.0, 133.4, 132.6, 132.2, 131.0, 129.8, 128.9, 128.9, 128.5, 127.6, 127.3, 126.6, 126.4, 124.4, 123.8, 123.0, 75.1, 38.5. HRMS (ESI+): m/z calcd for $C_{19}H_{13}N_3$ $[M+H]^+$: 284.1182, found 284.1187.

5-Ethyl-4-methyl-1-(prop-2-yn-1-yl)-1*H*-1,2,3-triazole (158m): pentan-3-one (100 mg, 1.16 mmol), propargyl amine (128 mg, 2.32 mmol), 4-nitrophenyl azide (267 mg, 1.62 mmol), zinc acetate (213 mg, 1.16 mmol), 4 Å molecular sieves (40 mg) and DMF (0.4 mL). Reaction time is 24 h. The product was purified by flash column chromatography (CH_2Cl_2 followed by heptane/EtOAc = 4:1) affording **158m** (137 mg, 79% yield) as an off white semi-solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.06 (d, *J* = 2.6 Hz, 2H), 2.76 (q, *J* = 7.6 Hz, 2H), 2.44 (t, *J* = 2.6 Hz, 1H), 2.29 (s, 3H), 1.24 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.0, 134.6, 76.2, 74.5, 37.9, 16.1, 13.0, 10.5. HRMS (ESI+): m/z calcd for $C_8H_{11}N_3$ $[M+H]^+$: 150.1025, found 150.1022.

5-Methyl-1-(prop-2-yn-1-yl)-1*H*-1,2,3-triazole (158n): Acetone (71 mg, 1.21 mmol), propargyl amine (47.9 mg, 0.87 mmol), 4-nitrophenyl azide (100 mg, 0.60 mmol), zinc acetate (79 mg, 0.43 mmol), 4 Å molecular sieves (40 mg) and DMF (0.4 mL). Reaction time is 24 h. The product was purified by flash column chromatography (CH_2Cl_2 followed by heptane/EtOAc = 4:1) affording **158n** (56 mg, 76 % yield) as an off white semi-solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (s, 1H), 5.11 (d, *J* = 2.6 Hz, 2H), 2.47 (t, *J* = 2.6 Hz, 1H), 2.42 (d, *J* = 0.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.5, 133.0, 75.4, 74.8, 37.7, 8.5. HRMS (ESI+): m/z calcd for $C_6H_7N_3$ $[M+H]^+$: 122.0712, found 122.0705.

5-(Dibenzo[b,d]furan-2-yl)-1-(prop-2-yn-1-yl)-1*H*-1,2,3-triazole (158o): 1-(dibenzo[b,d]furan-2-yl)ethan-1-one (100 mg, 0.47 mmol), propargyl amine (52.4 mg, 0.95 mmol), 4-nitrophenyl azide (109 mg, 0.66 mmol), zinc acetate (87 mg, 0.47 mmol), 4 Å molecular sieves (40 mg) and DMF (0.4 mL). Reaction time is 36 h. The product was purified by flash column chromatography (CH_2Cl_2 followed by heptane/EtOAc = 6:4) affording **158o** (60 mg, 46 % yield) as an off white solid. m.p. 93 – 94 ˚C . ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (d, *J* = 1.4 Hz, 1H), 7.99 (dd, *J* = 7.7, 0.6 Hz, 1H), 7.82 (s, 1H), 7.73 – 7.69 (m, 1H), 7.66 – 7.58 (m, 2H), 7.57 – 7.51 (m, 1H), 7.41 (td, *J* = 7.6, 1.0 Hz, 1H), 5.17 (d, *J* = 2.6 Hz, 2H), 2.51 (t, *J* = 2.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.9, 156.8, 138.2, 133.3, 128.3, 127.8, 125.3, 123.5, 123.4, 121.4, 121.5, 121.0, 112.6, 112.1, 77.2, 75.0, 38.3. HRMS (ESI+): no mass detected.

3,6-Di-tert-butyl-9-(4-(1-(prop-2-yn-1-yl)-1*H*-1,2,3-triazol-5-yl)phenyl)-9H-carbazole (158p): 1-(4-(3,6-di-tert-butyl-9H-carbazol-9-yl)phenyl)ethan-1-one (100 mg, 0.25 mmol), propargyl amine (41.6 mg, 0.75 mmol), 4-nitrophenyl azide (61.9 mg, 0.37 mmol), zinc acetate (46.1 mg, 0.25 mmol), 4 Å molecular sieves (40 mg) and DMF (0.4 mL). Reaction time is 24 h. The product was purified by flash column chromatography (CH_2Cl_2 followed by heptane/EtOAc = 3:2) affording **158p** (61 mg, 53 % yield) as an off white solid. m.p. 220 – 221 ˚C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (d, *J* = 1.3 Hz, 2H), 7.86 (s, 1H), 7.76 (d, *J* = 2.0 Hz, 4H), 7.51 - 7.41 (m, 4H), 5.25 (d, *J* = 2.5 Hz, 2H), 2.53 (t, *J* = 2.5 Hz, 1H), 1.48 (s, 18H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.7, 139.9, 138.9, 137.5, 133.4, 130.3, 127.2, 124.7, 124.0, 123.9, 116.6, 109.2, 76.6, 75.2, 38.5, 34.9, 32.1. HRMS (ESI^+): m/z calcd for $C_{31}H_{32}N_4$ $[M+H]^+$: 461.2699, found 461.2692.

(1S,3aS,3bR,5aS,10aS,10bS,12aS)-10a,12a-Dimethyl-7-(prop-2-yn-1-yl)-1,2,3,3a,3b,4,5,5a,6,7,10,10a,10b,11,12,12a-hexadecahydrocyclopenta[7,8]phenanthro[2,3-d][1,2,3]triazol-1-ol (158q): 5α-Dihydrotestosterone (90 mg, 0.31 mmol), propargyl amine (34.1 mg, 0.62 mmol), 4-nitrophenyl azide (71.2 mg, 0.43 mmol), zinc acetate (56.9 mg, 0.31 mmol), 4 Å molecular sieves (40 mg) and DMF (0.4 mL). Reaction time is 24 h. The product was purified by flash

column chromatography (CH_2Cl_2 followed by heptane/EtOAc = 3:2) affording **158q** (63 mg, 57.5 % yield) as an off white solid. m.p. 198 – 199 ˚C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.05 (t, *J* = 2.5 Hz, 2H), 3.66 (t, *J* = 8.5 Hz, 1H), 2.86 (d, *J* = 15.5 Hz, 1H), 2.68 (dd, *J* = 15.9, 5.0 Hz, 1H), 2.45 (t, *J* = 2.6 Hz, 1H), 2.33 – 2.25 (m, 2H), 2.14 – 2.02 (m, 1H), 1.87 (dt, *J* = 12.4, 3.3 Hz, 1H), 1.79 – 1.72 (m, 1H), 1.72 – 1.57 (m, 5H), 1.53 – 1.36 (m, 4H), 1.34 – 1.22 (m, 1H), 1.12 (td, *J* = 12.8, 4.1 Hz, 1H), 1.04 – 0.85 (m, 3H), 0.77 (s, 3H), 0.74 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.0, 131.0, 82.0, 75.6, 74.7, 53.9, 50.9, 43.0, 42.3, 37.8, 36.9, 36.7, 36.2, 35.7, 31.3, 30.6, 29.0, 24.6, 23.6, 20.9, 11.8, 11.2. HRMS (ESI+): m/z calcd for $C_{22}H_{31}N_3O_1$ $[M+H]^+$: 354.2539, found 354.2532.

(1R,3aS,3bR,5aS,10aS,10bS,12aR)-10a,12a-Dimethyl-1-((R)-6-methylheptan-2-yl)-7-(prop-2-yn-1-yl)-1,2,3,3a,3b,4,5,5a,6,7,10,10a,10b,11,12,12a-hexadecahydrocyclopenta[7,8]phenanthro[2,3-d][1,2,3]triazole (158r): (5S,8R,9S,10S,13R,14S,17R)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)hexadecahydro-3*H*-cyclopenta[a]phenanthren-3-one (100 mg, 0.25 mmol), propargyl amine (28.5 mg, 0.51 mmol), 4-nitrophenyl azide (59.4 mg, 0.36 mmol), zinc acetate (47.4 mg, 0.25 mmol), 4 Å molecular sieves (40 mg) and DMF (0.4 mL). Reaction time is 24 h. The product was purified by flash column chromatography (CH_2Cl_2 followed by heptane/EtOAc = 3:2) affording **158r** (72 mg, 62% yield) as an off white solid. m.p. 132 – 133 ˚C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.11 – 5.01 (m, 2H), 2.85 (d, *J* = 15.2 Hz, 1H), 2.66 (dd, *J* = 15.6, 5.2 Hz, 1H), 2.44 (t, *J* = 2.6 Hz, 1H), 2.32 – 2.25 (m, 2H), 2.06 - 2.03 (m, 1H), 1.87 - 1.80 (m, 1H), 1.76 - 1.72 (m, 1H), 1.68 – 1.57 (m, 4H), 1.54 - 1.46 (m, 2H), 1.42 – 1.31 (m, 6H), 1.28 – 1.23 (m, 2H), 1.18 – 1.06 (m, 6H), 1.04 - 0.99 (m, 2H), 0.92 (d, *J* = 6.5 Hz, 3H), 0.87 (d, *J* = 2.6 Hz, 3H), 0.86 (d, *J* = 2.6 Hz, 3H), 0.73 (s, 3H), 0.68 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.2, 131.1, 77.4, 75.6, 74.7, 56.4, 53.8, 42.6, 42.3, 40.0, 39.6, 37.8, 36.8, 36.3, 36.2, 35.9, 35.7, 31.7, 29.1, 28.4, 28.2, 24.6, 24.4, 24.0, 23.0, 22.7 21.3, 18.8, 12.1, 11.8. HRMS (ESI+): m/z calcd for $C_{30}H_{47}N_3$ $[M+H]^+$: 450.3842, found 450.3844.

Carbazole porphyrin conjugate (160a): 3,6-di-tert-butyl-9-(4-(1-(prop-2-yn-1-yl)-1*H*-1,2,3-triazol-5-yl)phenyl)-9*H*-carbazole (69 mg, 0.15

mmol), Zn-TPP (192 mg, 0.18 mmol), $CuSO_4$ (1.195 mg, 0.00749 mmol), sodium (R)-2-((S)-1,2-dihydroxyethyl)-4-hydroxy-5-oxo-2,5-dihydrofuran-3-olate (3.26 mg, 0.02 mmol), *t*-BuOH:DCM:H_2O (1:1:1). Reaction time is 6 h. After the reaction was completed, the reaction mixture was extracted with DCM 3 times (3 X 100 mL). Dried over $MgSO_4$ and concentrated under reduced pressure to afford the desired product **160a** in 78 % yield (178 mg) as an off white solid. m.p. 253 – 254 ˚C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.10 (d, *J* = 4.6 Hz, 2H), 9.00 (s, 4H), 8.94 (d, *J* = 4.6 Hz, 2H), 8.30 (d, *J* = 7.9 Hz, 2H), 8.15 (d, *J* = 1.6 Hz, 4H), 8.11 (d, *J* = 1.6 Hz, 2H), 8.07 (d, *J* = 1.6 Hz, 2H), 7.83 (s, 2H), 7.78 (s, 1H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.40 – 7.34 (m, 4H), 7.23 (d, *J* = 8.7 Hz, 3H), 7.03 (d, *J* = 7.8 Hz, 2H), 6.77 (s, 1H), 5.59 (s, 2H), 4.82 (s, 2H), 1.54 (s, 36H), 1.52 (s, 18H), 1.40 (s, 18H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.7, 150.5, 150.2, 149.9, 148.8, 148.5, 144.6, 143.6, 142.7, 142.6, 142.1, 139.8, 138.7, 136.0, 135.2, 133.8, 132.2, 131.4, 130.4, 129.9, 126.8, 125.3, 123.9, 123.8, 123.6, 122.8, 122.4, 122.2, 120.9, 120.8, 119.5, 116.5, 109.2, 35.3, 35.2, 34.9, 32.1, 32.0, 31.9. HRMS (ESI+): m/z calcd for $C_{100}H_{109}N_{11}Zn$ $[M+H]^+$: 1528.8231, found 1528.8428.

1-(4-(4-(((1R,3aS,3bR,5aS,10aS,10bS,12aR)-10a,12a-Dimethyl-1-((R)-6-methylheptan-2-yl)-2,3,3a,3b,4,5,5a,6,10,10a,10b,11,12,12a-tetradecahydrocyclopenta[7,8]phenanthro[2,3-d][1,2,3]triazol-7(1*H*)-yl)methyl)-1H-1,2,3-triazol-1-yl)-5-(hydroxymethyl)tetrahydrofuran-2-yl)-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (160b): 158r (150 mg, 0.33 mmol), AZT (107 mg, 0.40 mmol), $CuSO_4$ (2.66 mg, 0.02 mmol), sodium (R)-2-((S)-1,2-dihydroxyethyl)-4-hydroxy-5-oxo-2,5-dihydrofuran-3-olate (7.27 mg, 0.04 mmol), *t*-BuOH:H_2O (1:1). Reaction time is 12 h. After the reaction was completed, the reaction mixture was extracted with DCM 3 times (3 X 100 mL), dried over $MgSO_4$ and concentrated under reduced pressure to afford the desired product **160b** in 84 % yield (201 mg) as an off white solid. m.p. 188 – 189 ˚C. ^{1}H NMR (400 MHz, DMSO) δ 11.34 (s, 1H), 8.32 (s, 1H), 7.80 (s, 1H), 6.41 (t, *J* = 6.5 Hz, 1H), 5.55 (s, 2H), 5.36 (dt, *J* = 10.4, 5.3 Hz, 1H), 5.27 (t, *J* = 5.0 Hz, 1H), 4.18 (d, *J* = 4.7 Hz, 1H), 3.73 – 3.57 (m, 2H), 2.62 – 2.50 (m, 4H),

2.20 (t, *J* = 14.7 Hz, 2H), 1.98 (d, *J* = 12.1 Hz, 1H), 1.80 (s, 4H), 1.65 (d, *J* = 10.8 Hz, 1H), 1.62 – 1.45 (m, 5H), 1.32 (s, 6H), 1.22 – 1.03 (m, 7H), 1.00 (d, *J* = 6.7 Hz, 2H), 0.90 (d, *J* = 6.2 Hz, 3H), 0.87 – 0.81 (m, 6H), 0.65 (s, 3H), 0.63 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 163.7, 150.4, 142.1, 136.2, 130.9, 123.5, 109.6, 84.4, 83.9, 60.7, 59.4, 55.8, 54.9, 52.8, 42.4, 42.0, 41.5, 39.5, 37.1, 36.2, 35.6, 35.6, 35.2, 35.0, 31.2, 28.4, 27.8, 27.4, 23.86, 23.7, 23.2, 22.6, 22.4, 20.7, 18.5, 12.2, 11.8, 11.4. HRMS (ESI+): m/z calcd for $C_{40}H_{60}N_8O_4$ $[M+H]^+$: 717.4809, found 717.4813.

2-(2-(2-(4-(((1R,3aS,3bR,5aS,10aS,10bS,12aR)-10a,12a-Dimethyl-1-((R)-6-methylheptan-2-yl)-2,3,3a,3b,4,5,5a,6,10,10a,10b,11,12,12a-tetradecahydrocyclopenta[7,8]phenanthro[2,3-d][1,2,3]triazol-7(1H)-yl)methyl)-1*H*-1,2,3-triazol-1-yl)ethoxy)ethoxy)ethan-1-ol (160c): 158r (150 mg, 0.33 mmol), 2-(2-(2-azidoethoxy)ethoxy)ethan-1-ol (70.1 mg, 0.40 mmol), $CuSO_4$ (2.66 mg, 0.02 mmol), sodium (R)-2-((S)-1,2-dihydroxyethyl)-4-hydroxy-5-oxo-2,5-dihydrofuran-3-olate (7.27 mg, 0.04 mmol), *t*-BuOH:H_2O:THF (1:1:1). Reaction time is 12 h. After the reaction was completed, the reaction mixture was extracted with DCM 3 times (3 X 100 mL), dried over $MgSO_4$ and concentrated under reduced pressure to afford the desired product **160c** in 67 % yield (143 mg). as an off white solid. m.p. 101 – 102 ˚C ^{1}H NMR (600 MHz, MeOD) δ 8.04 (s, 1H), 5.47 (s, 2H), 4.47 (s, 2H), 3.77 (d, *J* = 4.2 Hz, 2H), 3.56 – 3.52 (m, 2H), 3.48 (ddd, *J* = 8.2, 6.0, 2.9 Hz, 4H), 3.41 – 3.39 (m, 2H), 2.63 (s, 1H), 2.13 (s, 2H), 1.98 (d, *J* = 12.0 Hz, 1H), 1.82 – 1.73 (m, 1H), 1.67 – 1.64 (m, 1H), 1.58 – 1.48 (m, 3H), 1.46 - 1.40 (m, 3H), 1.34 – 1.24 (m, 6H), 1.22 – 1.12 (m, 2H), 1.12 – 0.98 (m, 6H), 0.98 – 0.89 (m, 2H), 0.86 (d, *J* = 6.4 Hz, 4H), 0.79 (d, *J* = 2.3 Hz, 3H), 0.78 (d, *J* = 2.3 Hz, 3H), 0.63 (s, 3H), 0.59 (s, 3H). ^{13}C NMR (101 MHz, MeOD) δ 126.1, 73.7, 71.4, 70.2, 62.2, 57.7, 55.0, 54.8, 51.5, 44.1, 43.6, 43.4, 41.3, 40.7, 37.7, 37.4, 37.2, 37.0, 36.9, 32.8, 29.9, 29.3, 29.2, 25.3, 25.0, 23.2, 23.0, 22.3, 19.3, 12.4, 12.0. HRMS (ESI+): m/z calcd for $C_{36}H_{60}N_6O_3$ $[M+H]^+$: 625.4799, found 625.4813.

(2R,3S,4R,5R)-2-((benzoyloxy)methyl)-5-(4-(((1S,3aS,3bR,5aS,10aS,10bS,12aS)-1-hydroxy-10a,12a-dimethyl-

2,3,3a,3b,4,5,5a,6,10,10a,10b,11,12,12a-tetradecahydrocyclopenta[7,8]phenanthro[2,3-d][1,2,3]triazol-7(1H)-yl)methyl)-1*H*-1,2,3-triazol-1-yl)tetrahydrofuran-3,4-diyl dibenzoate (160d): 158q (100 mg, 0.28 mmol), (2R,3R,4S,5R)-2-azido-5-((benzoyloxy)methyl)tetrahydrofuran-3,4-diyl dibenzoate (165 mg, 0.34 mmol), $CuSO_4$ (2.483 mg, 0.02 mmol), sodium (R)-2-((S)-1,2-dihydroxyethyl)-4-hydroxy-5-oxo-2,5-dihydrofuran-3-olate (6.16 mg, 0.03 mmol). *t*-BuOH:H_2O (1:1). Reaction time is 12 h. After the reaction was completed, the reaction mixture was extracted with DCM 3 times (3 X 100 mL). Dried over $MgSO_4$ and concentrated under reduced pressure to afford the desired product **160d** in 90 % yield (215 mg) as an off white solid. m.p. 123 – 124 ˚C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.0 Hz, 2H), 7.95 (dd, *J* = 13.0, 8.1 Hz, 4H), 7.81 (s, 1H), 7.56 (q, *J* = 7.5 Hz, 3H), 7.45 - 7.35 (m, 6H), 6.35 (d, *J* = 2.4 Hz, 1H), 6.26 – 6.22 (m, 1H), 6.13 (t, *J* = 5.7 Hz, 1H), 5.54 – 5.40 (m, 2H), 4.88 (dd, *J* = 9.3, 4.6 Hz, 1H), 4.77 (dd, *J* = 12.2, 3.2 Hz, 1H), 4.59 (dd, *J* = 12.2, 4.8 Hz, 1H), 3.65 (t, *J* = 8.4 Hz, 1H), 2.82 (d, *J* = 13.2 Hz, 1H), 2.69 (d, *J* = 14.8 Hz, 1H), 2.27 – 2.15 (m, 2H), 2.12 – 1.99 (m, 1H), 1.85 (d, *J* = 12.1 Hz, 1H), 1.75 – 1.52 (m, 6H), 1.48 – 1.22 (m, 5H), 1.10 (t, *J* = 11.3 Hz, 1H), 1.02 – 0.80 (m, 3H), 0.75 (s, 3H), 0.67 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2, 165.2, 165.1, 143.0, 134.0, 133.8, 133.5, 130.0, 129.9, 129.9, 129.4, 128.7, 128.7, 128.6, 128.5, 122.9, 90.5, 81.9, 81.3, 77.4, 75.2, 71.7, 63.8, 53.8, 50.9, 43.2, 43.0, 42.2, 36.8, 36.7, 36.2, 35.7, 31.2, 30.6, 29.81, 28.8, 24.4, 23.5, 20.9, 11.8, 11.2. HRMS (ESI+): m/z calcd for $C_{48}H_{52}N_6O_8$ $[M+H]^+$: 841.3919, found 841.3929.

((2R,3S,5R)-3-((4-Chlorobenzoyl)oxy)-5-(4-((5-phenyl-1H-1,2,3-triazol-1-yl)methyl)-1*H*-1,2,3-triazol-1-yl)tetrahydrofuran-2-yl)methyl 4-chlorobenzoate (160e): 5-phenyl-1-(prop-2-yn-1-yl)-1H-1,2,3-triazole (50 mg, 0.27 mmol), (2R,3S,5R)-5-azido-2-(((4-chlorobenzoyl)oxy)methyl)tetrahydrofuran-3-yl 4-chlorobenzoate (143 mg, 0.33 mmol), $CuSO_4$ (2.178 mg, 0.01 mmol), sodium (R)-2-((S)-1,2-dihydroxyethyl)-4-hydroxy-5-oxo-2,5-dihydrofuran-3-olate (5.95 mg, 0.03 mmol). *t*-BuOH:H_2O (1:1). Reaction time is 12 h. After the reaction was completed, the reaction mixture was extracted with DCM 3 times (3 X 100 mL), dried over $MgSO_4$ and concentrated under

reduced pressure to afford the desired product **160e** in 88% yield (148 mg) as an off white solid. m.p. 154 – 155 ˚C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 – 7.85 (m, 5H), 7.71 (s, 1H), 7.52 – 7.36 (m, 10H), 6.41 (t, *J* = 6.1 Hz, 1H), 5.80 (dd, *J* = 6.5, 3.3 Hz, 1H), 5.61 (s, 2H), 4.68 – 4.59 (m, 1H), 4.59 – 4.45 (m, 2H), 3.35 - 3.26 (m, 1H), 2.88 - 2.80 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.3, 165.0, 143.1, 140.3, 139.9, 131.2, 129.8, 129.3, 129.1, 129.0, 128.9, 127.8, 127.5, 126.4, 123.2, 88.8, 83.5, 75.1, 64.2, 43.4, 37.8. HRMS (ESI+): m/z calcd for $C_{30}H_{24}Cl_2N_6O_5$ $[M+H]^+$: 619.1257, found 619.1264.

4.5 Notes and References

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Chapter 5

Synthesis of polycyclic dihydroindoles by selective decomposition of bis(1,2,3-triazoles) mediated by rhodium-catalysis

Sampad Jana carried out the experiments, analyzed the data and wrote the manuscript.

5.1 Introduction

Substituted indoles are encountered in a vast number of heterocyclic molecules with a wide range of applications ranging from medicinal to material chemistry[1]. More specifically, 3,4-fused indoles and hapalindole alkaloid analogues are important pharmacophores found in nature, such as dehydrobufotenine, chanoclavine, lysergic acid, and cyclavine (Figure 9).[2] Generally, this type of fused indoles can be synthesized only via multistep procedures[2d,3]. Therefore, the biological properties of these type of fused heterocycles remain for the most part unexplored because of the difficulties in obtaining them in sufficient quantities. Hence, the development of atom economic one step synthetic strategies towards 3,4-fused indoles is highly desirable. In recent years, azavinylcarbenes derived from *N*-sulfonyl-1,2,3-triazoles have drawn considerable attention in the chemical community as a means towards the synthesis of various heterocycles which are otherwise very difficult to synthesize.[4,5,6] 1,2,3-Triazoles are known to be very stable heterocycles, however they can be decomposed to azavinylcarbenes by using appropriate substituents on the 1,2,3-triazole ring and a transition metal catalyst. In 2007, Gevorgyan was first to point out that 1,2,3-triazoles could be cleaved by transition metal catalysis to azavinylcarbene species, which was further used in various transformation.[4,5,6] Since then, a vast number of synthetic strategies have been discovered including transannulation, cyclopropanation, dehydrogenative rearrangements, C-H bond insertion, ring expansion, and ylide formation, in which 1-sulfonyl-1,2,3-triazoles have been used as a carbene precursor.[4,5,6]

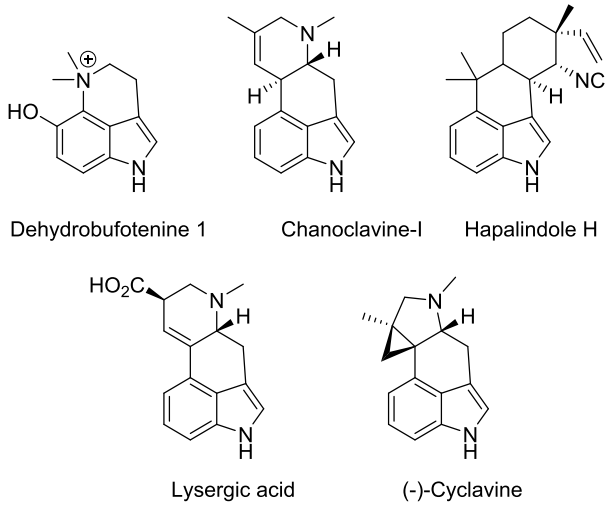
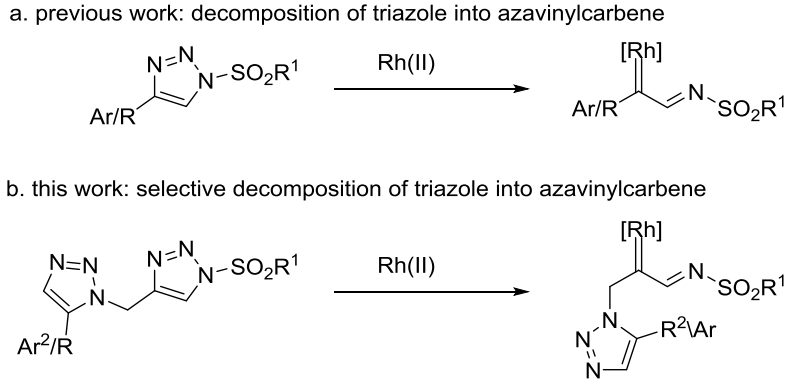


Figure 9 Representative bioactive molecules with 3,4-fused indole core

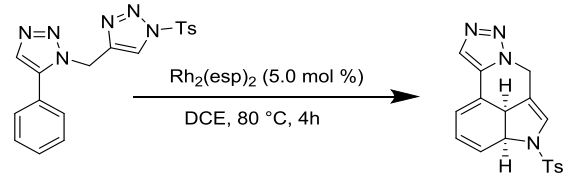


Scheme 35 Decomposition of triazole into azavinylcarbene

We have been working on the development of various synthetic strategies towards the synthesis of functionalized 1,2,3-triazoles.[7] Recently, we have reported a novel methodology towards the synthesis of propargyl substituted 1,2,3-triazoles, and further functionalization of these triazoles *via* Cu(I)-catalyzed click reaction resulted in the formation of unique *N,C*-linked bis(1,2,3-triazoles).[7a]

5.2 Result and discussion

In 2014 Murakami *et al.* reported an intramolecular dearomatizing annulation reaction of 4-(3-arylpropyl)-1,2,3-triazoles furnishing dihydroindole skeletons.[4k] Inspired by this report, we have anticipated that this reaction could be applied to the N,C-linked bis(1,2,3-triazoles) bearing the appropriate substituents (Scheme 35). The bis(1,2,3-triazole) **161a**, has been synthesized from *N*-propargyl-5-phenyltriazole with tosyl azide in presence of copper(I) thiophene-2-carboxylate (CuTc) catalyst. As we had hoped, our initial trial with **161a** in presence of Rh(II) leads to selective decomposition of the 1,4-disubstituted 1,2,3-triazole core, leading to a 3,4-fused dihydroindole **162a** via intramolecular [3 + 2]-annulation reactions. To the best of our knowledge, this is the first example of a selective decomposition of bis(1,2,3-triazoles) into azavinylcarbene in presence of a rhodium catalyst.



161a **162a**

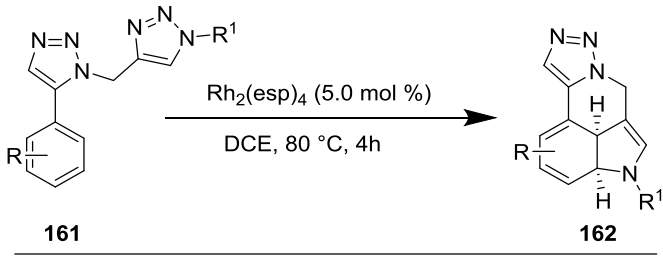
Entry	Catalyst	Temp (°C)	Time (h)	Solvent	Yield[b] (%)
1	$Rh_2(OAc)_4$	80	12	DCE	43
2	$Rh_2(OAc)_4$	80	4	DCE	46
3	$Rh_2(oct)_4$	80	4	DCE	51
4	$Rh_2(Piv)_4$	80	4	DCE	63
5	$Rh_2(tpa)_4$	80	4	DCE	49
6	**$Rh_2(esp)_2$**	**80**	**4**	**DCE**	**76**
7	$Rh_2(esp)_2$	60	4	DCE	57
8	$Rh_2(esp)_2$	100	4	DCE	66
9	$Rh_2(esp)_2$	80	4	Toluene	69
10	$Rh_2(esp)_2$	80	4	$CHCl_3$	70
11	$Rh_2(esp)_2$	80	4	Cyclohexane	63

Table 11 optimization of reaction conditions[a]

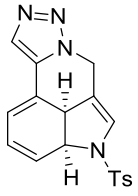
[a]All reactions were conducted on a 0.26 mmol scale in 4 mL solvent with 5 mol% catalyst under N_2 atmosphere. [b]isolated yield. $Rh_2(tpa)_4$ = Rh_2(triphenylacetate)$_4$, $Rh_2(esp)_2$ = bis[rhodium(α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid)].

After getting this promising result, we started to optimize this novel annulation reaction (Table 11). Triazole **161a** was treated with a catalytic amount of $Rh_2(OAc)_4$ in dry DCE at 80 °C under nitrogen atmosphere, and the desired fused indole **162a** was obtained in 43 % yield after 12 h. An increase in yield was observed when the reaction time was reduced to 4 h. Next, changing the catalyst from $Rh_2(OAc)_4$ to $Rh_2(esp)_2$ resulted in a significant increase in yield under the same conditions. Other catalyst, such as $Rh_2(oct)_4$ used by Murakami *et al.*[4k], $Rh_2(Piv)_4$, and $Rh_2(tpa)_4$ gave no better result. It was found that the yield decreased if the reaction was carried out at lower or higher temperature than 80 °C. While changing the solvent to toluene, $CHCl_3$ and cyclohexane resulted in slightly lower yield (Table 11).

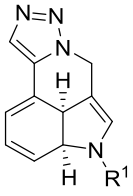
With the optimized conditions in hand, we started to investigate the role of the sulfonyl group substituents (Table 12). It was found that neither electron donating or electron withdrawing groups on the phenylsulfonyl ring had a significant effect on the outcome of the reaction (**162b** and **162c**). Next, the substitution effect on the 5-aryl ring was investigated (Table 12). Electron donating groups such as –Me (**162d**) and –OMe (**162e**) at the 4- position resulted in slightly lower yields, whereas an electron withdrawing group –F (**162f**) at the para position resulted in an increased yield. Similar trends were observed in case of the meta isomers. For instance, meta –F (**162h**) and $–CF_3$ (**162i**) afforded excellent yields as compared to meta –Me (**162g**) isomer.



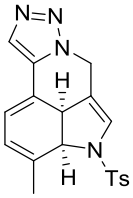
161 **162**



162a, 76%

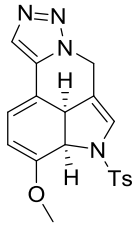


162b, 72%, R^1 = -SO_2-C_6H_4-pOMe

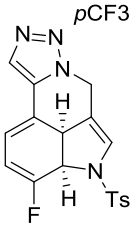


162d, 72 %

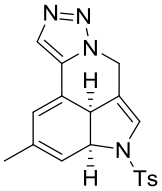
162c, 74%, R^1 = -SO_2-C_6H_4-*p*CF3



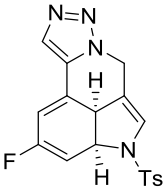
162e, 69 %



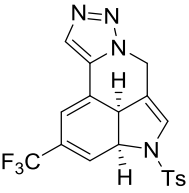
162f, 81 %



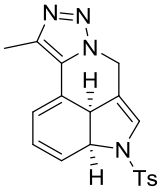
162g, 71 %



162h, 86 %



162i, 78 %



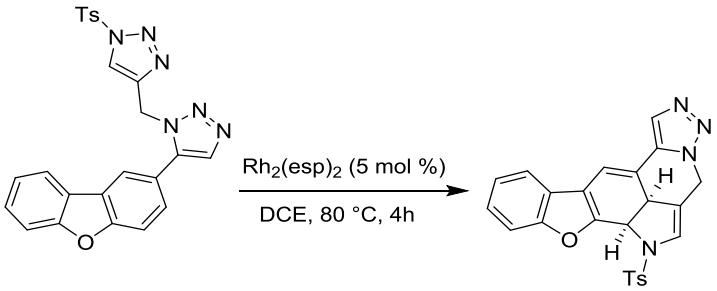
162j, 73 %

Table 12 Scope of dearomatizing trans annulation reaction of bis(1,2,3-triazoles)[a]

[a]General conditions: **161** (0.23 mmol), and $Rh_2(esp)_2$ (0.012 mmol), were heated in DCE (4 mL) at 80 °C for 4h unless otherwise noted.

In order to prove the generality of this reaction, in addition to the transannulation reaction onto different substituted phenyl groups, the use of heterocyclic dibenzofuran was also investigated (Scheme 36). Substrate **161k** underwent Rh(II)-catalyzed intramolecular cyclization to give the corresponding polyheterocyclic products **162k** in good yield.

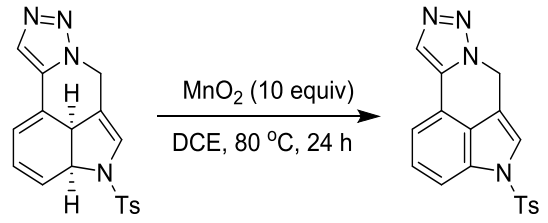
3,4-Fused indoles alkaloid analogues are interesting pharmacophores which could be accessible via oxidative aromatization of dihydroindole. Similar to Murakami *et al.*[4k] the oxidation reaction of 3,4-dihydroindole **162a** was carried out with MnO_2. This afforded the triazole-fused alkaloid analogue **163** in excellent yield (Scheme 4).



161k **162k**, 63%

Scheme 36 use of benzofuran in transannulation reaction towards **162k**

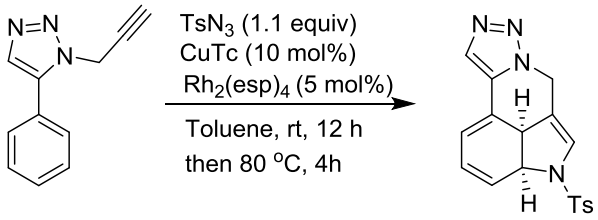
The synthetic utility of the Rh(II)-catalyzed selective 1,2,3-triazole decomposition and annulation reaction was further exemplified by a one-pot synthesis of 3,4-fused dihydroindole **162a** starting from propargyl triazole **164** in moderate yield (Scheme 38). Thus, in this way the interesting 1,2,3-triazole derived (dihydro)indole alkaloid analogues are accessible in a few reaction steps.



162a **163,** 89%

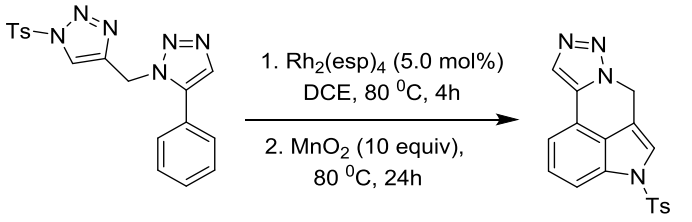
Scheme 37. Formation of fused indole derivative

A sequential one-pot synthesis of fused indole **163** was also carried out starting from bis(1,2,3-triazoles) **161a**. A mixture of bis(1,2,3-triazole) **161a** and $Rh_2(esp)_2$ was heated at 80 °C in DCE for 4h to form the dihydroindole. Subsequently, MnO_2 was added to the same reaction tube, which was further stirred at 80 °C for 24h to afford fused indole of bis(1,2,3-triazole) **163** in good yield. Thus the sequential one-pot reaction provides an easy access to triazole fused indole **163** in good yield (Scheme 39).



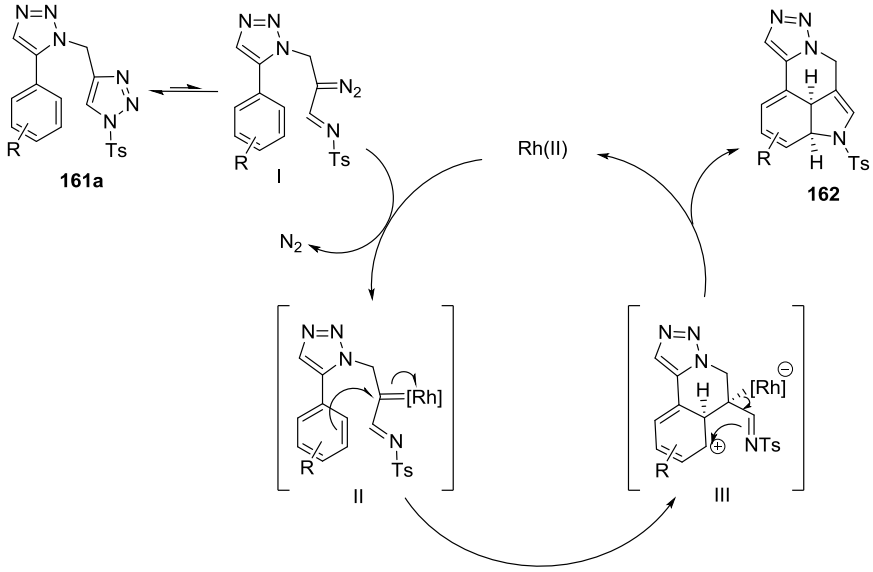
164 **162a,** 48%

Scheme 38 One-pot procedure starting from propargyl triazoles



161a **163,** 66 %

Scheme 39 One-pot procedure to access triazole fused indole from bis(1,2,3-triazole)



Scheme 40 Proposed reaction mechanism

A reaction mechanism is postulated on the basis of the previous literature reports[4-6] (Scheme 40). Triazole **161a** is in equilibrium with ring-chain tautomer α-diazo imine **I**, which subsequently reacts with Rh(II) affording α-imino rhodium carbene complex **II** and releases molecular dinitrogen. Then, intramolecular nucleophilic attack occurs of the phenyl at the electrophilic carbene center in a 6-exo mode to generate zwitterionic species **III**. In a final step, the anionic rhodium of **III** undergoes elimination which drives the final cyclization step, leading to final product **162a** and regenerating the Rh(II)-catalytic species.

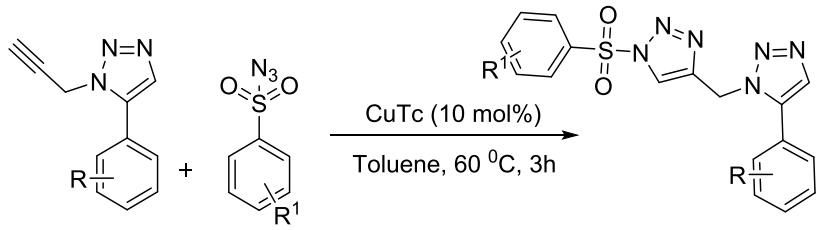
5.3 Conclusion

In conclusion, we have disclosed an unprecedented selective decomposition of bis(1,2,3-triazoles) by a Rh(II)-catalyzed [3 + 2]-intramolecular annulation reaction which leads to the formation of 3,4-fused indoles. Extension of this protocol to heterocycles led to

interesting polyfused 1,2,3-triazole derivatives. This protocol presents a simple, one-step, and atom economic efficient method for the synthesis of 1,2,3-triazole fused dihydroindoles and indoles, which could so far not be synthesized by other means. Further applications of these products in medicinal chemistry are in progress and will be reported in due course.

5.4 Experimental Section

5.4.1 General procedure for preparation of bis-triazoles.



A flame dried tube was charged with the appropriate propargyl triazole (0.66 mmol) , CuTc (0.06 mmol), and tosyl azide (0.73 mmol) in dry toluene(2 mL) under N_2 atmosphere. The resulted mixture was heated at 60 °C for 3 h. After consumption of the starting product as apparent from TLC analysis, the crude reaction mixture was concentrated *in vacuo*, and the product was isolated by flash column chromatography (EtOAc: heptane 1:1) to obtain pure product.

5.4.1.1 Charactarization data

5-Phenyl-1-((1-tosyl-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-1,2,3-triazole(161a): 83% Yield, Off white solid, m.p. 90 - 91 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.98 (d, *J* = 8.4 Hz, 2H), 7.73 (s, 1H), 7.51 – 7.42 (m, 5H), 7.39 (d, *J* = 8.1 Hz, 2H), 5.63 (s, 2H), 2.46 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.65, 142.11, 138.31, 132.82, 132.38, 130.48, 129.71, 129.12, 128.86, 128.67, 126.06, 123.29, 42.94, 21.73. HRMS (ESI+) m/z calcd for $C_{18}H_{16}N_6O_2S$ $[M + H]^+$ 381.1128, found 381.1162.

1-((4-Methoxyphenyl)sulfonyl)-4-((5-phenyl-1*H*-1,2,3-triazol-1-yl)methyl)-1*H*-1,2,3-triazole (161b): 65% Yield, off white solid, m.p. 260 - 261 °C, ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.14 (s, 1H), 8.04 (d, *J* = 9.0 Hz, 2H), 7.73 (s, 1H), 7.50 – 7.48 (m, 3H), 7.46 – 7.44 (m, 2H), 7.04 (d, *J* = 9.0 Hz, 2H), 5.63 (s, 2H), 3.89 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.75, 142.31, 138.57, 133.13, 131.59, 130.00, 129.42, 129.14, 126.57, 126.31, 123.26, 115.34, 114.38, 56.12, 43.24. HRMS (ESI+) m/z calcd for $C_{18}H_{16}N_6O_3S$ $[M + H]^+$ 397.10772, found 397.1034.

5-Phenyl-1-((1-((4-(trifluoromethyl)phenyl)sulfonyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-1,2,3-triazole (161c): 78% Yield, off white solid, m.p. 239 - 240 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (d, *J* = 8.3 Hz, 2H), 8.22 (s, 1H), 7.89 (d, *J* = 8.3 Hz, 2H), 7.74 (s, 1H), 7.51 – 7.43 (m, 5H), 5.65 (s, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 152.20, 141.32, 137.57, 132.80, 129.41, 129.06, 128.87, 128.65, 128.45, 126.50, 126.33, 125.07, 124.90, 124.88, 123.27, 43.14. HRMS (ESI+) m/z calcd for $C_{18}H_{13}F_3N_6O_2S$ $[M + H]^+$ 435.08454, found 435.0839

5-(4-Tolyl)-1-((1-tosyl-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-1,2,3-triazole (161d): 58% Yield, Off white solid, m.p. 135 - 136 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.98 (d, *J* = 8.3 Hz, 2H), 7.71 (s, 1H), 7.39 (d, *J* = 8.2 Hz, 2H), 7.35 – 7.29 (m, 4H), 5.62 (s, 2H), 2.46 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 147.81, 142.47, 140.24, 138.65, 132.93, 132.72, 130.68, 130.09, 129.01, 128.97, 123.40, 123.22, 43.18, 22.00, 21.48. HRMS (ESI+) m/z calcd for C19H18N6O2S $[M + H]^+$ 395.1284, found 395.1285.

5-(4-Methoxyphenyl)-1-((1-tosyl-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-1,2,3-triazole (161e): 89% Yield, Off white solid, m.p. 146 - 150 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.99 (d, *J* = 8.5 Hz, 2H), 7.68 (s, 1H), 7.42 – 7.34 (m, 4H), 7.00 (d, *J* = 8.8 Hz, 2H), 5.61 (s, 2H), 3.86 (s, 3H), 2.46 (s, 3H). ^{13}C NMR (75 MHz, DMSO) δ 160.04, 145.48, 141.44, 137.82, 137.44, 132.43, 130.13, 128.15, 125.53, 118.56, 114.56, 55.35, 43.01, 20.82. HRMS (ESI+) m/z calcd for $C_{19}H_{18}N_6O_3S$ $[M + H]^+$ 411.1233, found 411.1232.

5-(4-Fluorophenyl)-1-((1-tosyl-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-1,2,3-triazole (161f): 59% Yield, Off white solid, m.p. 99 - 100 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.99 (d, *J* = 8.5 Hz, 2H), 7.70 (s, 1H), 7.50 – 7.44 (m, 2H), 7.40 (d, *J* = 8.1 Hz, 2H), 7.18 (t, *J* = 8.6 Hz, 2H), 5.60 (s, 2H), 2.46 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.92, 142.17, 137.65, 132.60, 131.31, 131.19, 130.72, 129.04, 123.49, 122.33, 116.79, 116.50, 43.05, 22.02. HRMS (ESI+) m/z calcd for $C_{18}H_{15}FN_6O_2S$ $[M + H]^+$ 399.1033, found 399.1033.

5-(3-Tolyl)-1-((1-tosyl-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-1,2,3-triazole (161g): 66% Yield, Off-white semi solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.99 (d, *J* = 8.5 Hz, 2H), 7.71 (s, 1H), 7.42 – 7.34 (m, 3H), 7.30 (s, 1H), 7.23 (d, *J* = 6.8 Hz, 2H), 5.63 (s, 2H), 2.46 (s, 3H), 2.40 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.08, 140.93, 139.74, 137.88, 131.99, 130.03, 129.56, 129.33, 129.18, 128.65, 126.48, 126.01, 123.46, 44.41, 21.44. HRMS (ESI+) m/z calcd for $C_{19}H_{18}N_6O_2S$ $[M + H]^+$ 395.1284, found 395.1283.

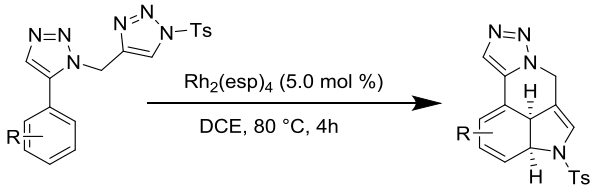
5-(3-Fluorophenyl)-1-((1-tosyl-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-1,2,3-triazole (161h): 72% Yield, Off white solid, m.p. 118 - 119 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.99 (d, *J* = 8.5 Hz, 2H), 7.74 (s, 1H), 7.48 (td, *J* = 7.9, 5.8 Hz, 1H), 7.40 (d, *J* = 8.1 Hz, 2H), 7.29 – 7.25 (m, 1H), 5.63 (s, 2H), 2.46 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.43, 161.13, 141.20, 140.73, 138.24, 131.52, 131.41, 129.21, 128.87, 126.17, 125.90, 125.35, 118.08, 117.81, 116.76, 116.45, 44.06, 21.39. HRMS (ESI+) m/z calcd for $C_{18}H_{15}FN_6O_2S$ $[M + H]^+$ 399.1033, found 399.1030.

1-Tosyl-4-((5-(3-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazol-1-yl)methyl)-1*H*-1,2,3-triazole(161i): 70% Yield, Off white solid, m.p. 83 - 84 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.24 (s, 1H), 8.00 (d, *J* = 8.5 Hz, 2H), 7.81 – 7.72 (m, 4H), 7.70 – 7.61 (m, 1H), 7.40 (d, *J* = 8.1 Hz, 2H), 5.61 (s, 2H), 2.46 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 147.95, 141.90, 137.22, 133.52, 132.64, 132.52, 130.74, 130.10, 129.07, 127.28, 126.79, 126.13, 123.52, 43.20, 22.02. HRMS (ESI+) m/z calcd for $C_{19}H_{15}F_3N_6O_2S$ $[M + H]^+$ 449.1001, found 449.0997.

4-Methyl-5-phenyl-1-((1-tosyl-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-1,2,3-triazole (161j): 79% Yield, Off white solid, m.p. 131 - 132 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.98 (d, *J* = 8.4 Hz, 2H), 7.51 – 7.47 (m, 3H), 7.39 (d, *J* = 8.2 Hz, 2H), 7.35 – 7.29 (m, 2H), 5.52 (s, 2H), 2.46 (s, 3H), 2.32 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 147.77, 142.57, 141.53, 134.91, 132.76, 130.66, 129.67, 129.34, 128.98, 126.78, 123.21, 53.56, 43.37, 21.98, 10.79. HRMS (ESI+) m/z calcd for C19H18N6O2S $[M + H]^+$ 395.12846, found 395.1269.

5-(Dibenzo[b,d]furan-2-yl)-1-((1-tosyl-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-1,2,3-triazole(161k): 72% Yield, Off white solid, m.p. 180 - 181 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (s, 1H), 8.13 – 8.11 (m, 1H), 8.01 – 7.96 (m, 3H), 7.80 (s, 1H), 7.69 – 7.60 (m, 2H), 7.56 – 7.50 (m, 2H), 7.40 – 7.36 (m, 3H), 5.68 (s, 2H), 2.45 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.86, 156.79, 147.88, 142.44, 132.67, 130.72, 129.02, 128.31, 128.10, 125.43, 123.62, 123.46, 121.85, 121.24, 120.76, 119.34, 112.72, 112.07, 43.11, 22.02. HRMS (ESI+) m/z calcd for $C_{24}H_{18}N_6O_3S$ $[M + H]^+$ 471.1233, found 471.1230.

5.4.2 General synthesis for Rh(II) catalyzed annulation reaction:



A flame dried reaction tube, fitted with rubber septum, was charged with triazole **161a – 161i** (0.263 mmol) and $Rh_2(esp)_2$ (0.013 mmol) at ambient temperature. The reaction tube was then evacuated and filled with argon three times before adding DCE (4 mL). The reaction mixture was then heated at 80 °C for 4h. After consumption of the starting product apparent from TLC analysis, the reaction mixture was cooled to room temperature. The crude reaction mixture was concentrated *in*

vacuo, and the product was isolated by flash column chromatography (ACN:DCM 1:20)to obtain pure product **162a - 162i**.

5.4.2.1 Characterization data

(3aS,3a1R)-4-Tosyl-3a,3a1,4,6-tetrahydropyrrolo[4,3,2-de][1,2,3]triazolo[5,1-a]isoquinoline (162a): 76% Yield, Off white solid, m.p. 203 - 204 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.72 (d, *J* = 8.3 Hz, 2H), 7.39 (d, *J* = 8.1 Hz, 2H), 6.66 (t, *J* = 1.7 Hz, 1H), 6.31 – 6.24 (m, 2H), 6.21 – 6.15 (m, 1H), 5.24 (d, *J* = 14.7 Hz, 1H), 5.02 (d, *J* = 14.6 Hz, 1H), 4.43 (dd, *J* = 13.6, 5.1 Hz, 1H), 3.73 (d, *J* = 13.6 Hz, 1H), 2.47 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.83, 134.50, 132.33, 130.19, 130.13, 129.39, 128.03, 126.08, 122.84, 120.33, 118.60, 113.14, 56.21, 45.60, 41.81, 21.79.

(3aS,3a1R)-4-((4-Methoxyphenyl)sulfonyl)-3a,3a1,4,6-tetrahydropyrrolo[4,3,2-de][1,2,3]triazolo[5,1-a]isoquinoline (162b): 72% Yield, Off white solid, m.p. 175 - 176 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 – 7.75 (m, 3H), 7.05 (d, *J* = 8.9 Hz, 2H), 6.65 (s, 1H), 6.31 – 6.23 (m, 2H), 6.17 (dd, *J* = 9.4, 5.1 Hz, 1H), 5.24 (d, *J* = 14.7 Hz, 1H), 5.02 (d, *J* = 14.6 Hz, 1H), 4.43 (dd, *J* = 13.6, 5.2 Hz, 1H), 3.90 (s, 3H), 3.74 (d, *J* = 13.7 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.81, 134.52, 130.24, 130.19, 129.40, 126.85, 126.06, 122.90, 120.35, 118.61, 114.73, 113.10, 56.19, 55.87, 45.62, 41.84. HRMS (ESI+) m/z calcd for $C_{18}H_{16}N_4O_3S$ $[M + H]^+$ 369.1015, found 369.1015.

(3aS,3a1R)-4-((4-(Trifluoromethyl)phenyl)sulfonyl)-3a,3a1,4,6-tetrahydropyrrolo[4,3,2-de][1,2,3]triazolo[5,1-a]isoquinoline (162c): 74% Yield, Off white solid, m.p. 191 - 192 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.2 Hz, 2H), 7.87 (d, *J* = 8.3 Hz, 2H), 7.78 (s, 1H), 6.68 (t, *J* = 1.8 Hz, 1H), 6.33 – 6.25 (m, 2H), 6.18 (ddd, *J* = 8.9, 5.2, 1.8 Hz, 1H), 5.26 (d, *J* = 14.7 Hz, 1H), 5.08 – 5.00 (m, 1H), 4.50 (dd, *J* = 13.6, 5.2 Hz, 1H), 3.79 (d, *J* = 13.7 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 139.36, 135.51, 135.29, 134.35, 129.50, 129.36, 128.44, 126.76, 126.74, 126.62, 124.11, 122.01, 120.37, 118.54, 114.02, 56.55, 45.53, 41.89. HRMS (ESI+) m/z calcd for $C_{18}H_{13}F_3N_4O_2S$ $[M + H]^+$ 407.07839, found 407.0776.

(3aR,3a1R)-3-Methyl-4-tosyl-3a,3a1,4,6-tetrahydropyrrolo[4,3,2-de][1,2,3]triazolo[5,1-a]isoquinoline (162d): 72% Yield, Off white semi-solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, *J* = 7.6 Hz, 3H), 7.38 (d, *J* = 8.0 Hz, 2H), 6.76 (t, *J* = 1.7 Hz, 1H), 6.23 (dd, *J* = 6.0, 2.1 Hz, 1H), 6.03 (d, *J* = 5.1 Hz, 1H), 5.28 – 5.20 (m, 1H), 5.06 – 4.96 (m, 1H), 4.25 (d, *J* = 12.3 Hz, 1H), 3.64 (d, *J* = 12.3 Hz, 1H), 2.47 (s, 3H), 2.19 – 2.14 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.33, 144.82, 132.38, 131.76, 131.45, 130.06, 128.20, 124.16, 119.57, 117.93, 114.50, 61.90, 45.45, 43.48, 23.65, 21.80. HRMS (ESI+) m/z calcd for $C_{19}H_{18}N_4O_2S$ $[M + H]^+$ 367.1223, found 367.1216.

(3aR,3a1R)-3-Methoxy-4-tosyl-3a,3a1,4,6-tetrahydropyrrolo[4,3,2-de][1,2,3]triazolo[5,1-a]isoquinoline (162e): 69% Yield, Off white solid, m.p. 195 - 196 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.3 Hz, 2H), 7.69 (s, 1H), 7.36 (d, *J* = 8.0 Hz, 2H), 6.84 (t, *J* = 1.6 Hz, 1H), 6.29 (dd, *J* = 6.6, 2.4 Hz, 1H), 5.29 – 5.20 (m, 2H), 5.08 – 4.96 (m, 1H), 4.28 (d, *J* = 11.9 Hz, 1H), 3.88 – 3.78 (m, 1H), 3.53 (s, 3H), 2.45 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.27, 144.38, 134.79, 133.47, 131.48, 129.73, 128.39, 128.14, 119.43, 113.62, 111.39, 96.12, 60.08, 55.33, 45.40, 44.65, 21.71. HRMS (ESI+) m/z calcd for $C_{19}H_{18}N_4O_3S$ $[M + H]^+$ 383.1172, found 383.1162.

(3aR,3a1R)-3-Fluoro-4-tosyl-3a,3a1,4,6-tetrahydropyrrolo[4,3,2-de][1,2,3]triazolo[5,1-a]isoquinoline (162f): 81% Yield, Off white solid, m.p. 76 - 77 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 – 7.74 (m, 3H), 7.39 (d, *J* = 8.1 Hz, 2H), 6.80 (t, *J* = 1.7 Hz, 1H), 6.22 (ddd, *J* = 6.8, 4.6, 2.4 Hz, 1H), 5.91 (dd, *J* = 10.9, 6.6 Hz, 1H), 5.26 (d, *J* = 14.5 Hz, 1H), 5.05 – 4.97 (m, 1H), 4.38 (dd, *J* = 12.7, 8.2 Hz, 1H), 3.99 (d, *J* = 12.7 Hz, 1H), 2.47 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.09, 154.39, 145.08, 134.00, 132.25, 131.43, 130.19, 129.31, 128.32, 117.49, 117.43, 117.21, 117.15, 116.19, 115.97, 111.69, 111.67, 105.97, 105.76, 77.16, 57.65, 57.38, 46.06, 45.99, 45.33, 21.82. HRMS (ESI+) m/z calcd for $C_{18}H_{15}FN_4O_2S$ $[M + H]^+$ 371.0972, found 971.0982.

(3aS,3a1R)-2-Methyl-4-tosyl-3a,3a1,4,6-tetrahydropyrrolo[4,3,2-de][1,2,3]triazolo[5,1-a]isoquinoline (162g): 71% Yield, Off white semi-solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.71 (d, *J* = 8.3 Hz, 2H), 7.38 (dd, *J* = 8.5, 0.6 Hz, 2H), 6.64 (t, *J* = 1.8 Hz, 1H), 6.16 (d, *J* = 2.0 Hz, 1H), 5.93 – 5.86 (m, 1H), 5.23 (d, *J* = 14.6 Hz, 1H), 5.05 – 4.95 (m, 1H), 4.40 (ddd, *J* = 13.3, 5.5, 1.1 Hz, 1H), 3.64 (d, *J* = 13.2 Hz, 1H), 2.46 (s, 3H), 1.92 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.69, 134.47, 134.44, 132.34, 130.10, 130.04, 129.74, 129.25, 127.96, 126.48, 122.57, 120.53, 117.55, 113.17, 57.16, 45.61, 41.50, 22.10, 21.75. HRMS (ESI+) m/z calcd for $C_{19}H_{18}N_4O_2S$ $[M + H]^+$ 367.1223, found 367.1219.

(3aR,3a1R)-2-Fluoro-4-tosyl-3a,3a1,4,6-tetrahydropyrrolo[4,3,2-de][1,2,3]triazolo[5,1-a]isoquinoline (162h): 88% Yield, Off white solid, m.p. 171 - 172 °C, ^{1}H NMR (300 MHz, DMSO) δ 8.15 (s, 1H), 7.78 (d, *J* = 8.3 Hz, 2H), 7.51 (d, *J* = 8.0 Hz, 2H), 6.87 (s, 1H), 6.62 – 6.55 (m, 1H), 5.67 (dd, *J* = 12.6, 5.9 Hz, 1H), 5.33 (d, *J* = 14.3 Hz, 1H), 5.08 (d, *J* = 14.2 Hz, 1H), 4.55 (dt, *J* = 13.1, 5.6 Hz, 1H), 4.05 (d, *J* = 12.9 Hz, 1H), 2.43 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.74, 158.06, 145.02, 143.69, 139.28, 133.30, 133.28, 132.38, 130.60, 130.27, 130.13, 129.83, 127.96, 126.56, 124.94, 124.87, 114.80, 114.54, 111.85, 99.11, 98.97, 57.40, 57.32, 45.65, 42.22, 21.80. HRMS (ESI+) m/z calcd for $C_{18}H_{15}FN_4O_2S$ $[M + H]^+$ 371.097, found 371.0959.

(3aS,3a1R)-4-Tosyl-2-(trifluoromethyl)-3a,3a1,4,6-tetrahydropyrrolo[4,3,2-de][1,2,3]triazolo[5,1-a]isoquinoline (162i): 78% Yield, Off white solid, m.p. 68 - 69 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.73 (d, *J* = 8.3 Hz, 2H), 7.40 (d, *J* = 8.0 Hz, 2H), 6.70 – 6.61 (m, 2H), 6.33 (d, *J* = 1.9 Hz, 1H), 5.32 – 5.23 (m, 1H), 5.05 (d, *J* = 14.8 Hz, 1H), 4.66 – 4.53 (m, 1H), 3.80 (d, *J* = 13.9 Hz, 1H), 2.48 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 145.32, 132.03, 130.36, 130.20, 129.85, 129.64, 129.43, 128.05, 126.58, 123.50, 123.26, 123.12, 123.08, 121.70, 113.17, 112.50, 55.15, 45.57, 41.96, 21.81. HRMS (ESI+) m/z calcd for $C_{19}H_{15}F_3N_4O_2S$ $[M + H]^+$ 421.0940, found 421.0926.

(3aS,3a1R)-10-Methyl-4-tosyl-3a,3a1,4,6-tetrahydropyrrolo[4,3,2-de][1,2,3]triazolo[5,1-a]isoquinoline (162j): 73% Yield, Off white

solid, m.p. 111 - 112 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.3 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 6.63 (t, *J* = 1.7 Hz, 3H), 6.29 (dd, *J* = 9.6, 6.0 Hz, 1H), 6.22 – 6.12 (m, 2H), 5.18 (d, *J* = 14.7 Hz, 1H), 5.01 – 4.92 (m, 1H), 4.39 (dd, *J* = 13.6, 5.2 Hz, 1H), 3.70 (d, *J* = 13.6 Hz, 1H), 2.46 (s, 3H), 2.40 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) 144.72, 139.91, 132.13, 130.11, 129.64, 129.60, 127.94, 126.15, 122.12, 121.31, 117.73, 113.39, 56.25, 45.57, 42.14, 21.70, 12.05. HRMS (ESI+) m/z calcd for $C_{19}H_{18}N_4O_2S$ $[M + H]^+$ 367.1223, found 367.1216.

(2a1R,13bR)-1-Tosyl-1,2a1,3,13b-tetrahydrobenzofuro[2,3-g]pyrrolo[4,3,2-de][1,2,3]triazolo[5,1-a]isoquinoline (162k): 63% Yield, Off white solid, m.p. 195 - 196 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.81 (dd, *J* = 8.3, 1.8 Hz, 2H), 7.60 (d, *J* = 7.4 Hz, 1H), 7.53 (d, *J* = 7.8 Hz, 1H), 7.40 – 7.36 (m, 1H), 7.34 – 7.29 (m, 3H), 6.92 (d, *J* = 2.4 Hz, 1H), 6.84 (d, *J* = 1.7 Hz, 1H), 5.35 – 5.06 (m, 3H), 4.17 (d, *J* = 12.7 Hz, 1H), 2.40 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.82, 147.01, 144.83, 133.02, 131.01, 130.00, 129.83, 128.24, 126.57, 125.75, 124.34, 123.63, 119.42, 118.34, 115.79, 114.30, 112.27, 111.76, 55.36, 46.56, 45.51, 21.75. HRMS (ESI+) m/z calcd for $C_{24}H_{18}N_4O_3S$ $[M + H]^+$ 443.1172, found 443.1181.

5.4.3 Oxidative aromatization reaction:

A flame dried reaction tube was charged with dihydroindole **162a** (100 mg, 0.284 mmol), MnO_2 (123 mg, 1.419 mmol) in DCE (2 mL). The reaction mixture was then heated at 80 °C for 24 h. After the completion of the reaction, the solvent was evaporated in *vacuo*. The crude reaction mixture was then directly purified by flash column chromatography (ACN: DCM 1:20) to afford fused indole **163** as a off white solid (79mg, 89 %).

4-Tosyl-4,6-dihydropyrrolo[4,3,2-de][1,2,3]triazolo[5,1-a]isoquinoline (163): 89% Yield, Off white solid, m.p. 210 - 211 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.87 (dd, *J* = 5.4, 3.5 Hz, 1H), 7.81 (d, *J* = 8.4 Hz, 2H), 7.50 (t, *J* = 1.9 Hz, 1H), 7.40 (d, *J* = 2.1 Hz, 1H), 7.39 (s, 1H), 7.26 (d, *J* = 8.0 Hz, 2H), 5.82 (d, *J* = 1.9 Hz, 2H), 2.36 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 145.69, 135.15, 133.01, 132.27, 130.25,

128.49, 126.98, 126.97, 126.92, 125.62, 120.97, 117.30, 117.02, 114.28, 112.17, 45.67, 21.73. HRMS (ESI+) m/z calcd for $C_{18}H_{14}N_4O_2S$ $[M + H]^+$ 351.0910, found 351.0911.

5.5 Notes and references

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Chapter 6
Application of the triazolization reaction to afford derivatives of dihydroartemisinin having anti-HIV activity

Sampad Jana planned the experiments, analyzed the data and wrote the manuscript.

6.1 Introduction

The human immunodeficiency virus (HIV), the causative agent of the acquired immunodeficiency syndrome (AIDS), has been plaguing the human race for more than thirty years.[1] According to the global statistics of UNAIDS, it has been estimated that globally 36.7 million people were suffering from HIV/AIDS in 2015.[2] Even though more than thirty drugs targeting different steps of the viral life cycle are either approved or in clinical stages to treat HIV/AIDS,[2] a cure remains elusive. Moreover, emergence of HIV strains that are no longer sensitive to the drug cocktails employed leading to inability to completely block the viral replication.[3] Thus, finding new anti-HIV agents that are less toxic and more effective in targeting HIV reservoirs in the body is still needed. Artemisinin is a naturally occurring 1,2,4-trioxane sesquiterpene, first isolated in 1972 from a Chinese medicinal plant that has been used as a treatment for fever for many centuries.[4] Reduction of the carbonyl group of artemisinin leads to the synthesis of dihydroartemisinin in high yields without disrupting the unusual peroxide linkage of artemisinin which has in turn led to the development of a series of semi-synthetic first-generation derivatives including the oil soluble artemether and arteether, and water soluble sodium artesunate.[6] Derivatives of artemisinin have shown an improved potency as antimalarial, anticancer and antiviral agents as compared to artemisinin itself.[5,6,7] Furthermore, derivatives of dihydroartemisinin are found to have anti-proliferative, antibacterial, antiviral, and immunosuppressive activities.[8-21] Even though it displays a high activity profile, dihydroartemisinin does suffer some drawbacks such as neurotoxicity in animal models, short pharmacological half-life, and recrudescence of the disease.[22, 23]

Artemisnin and derivatives of artemisnin are also well known for the anti-viral activity.[23b] However, the shortcomings of the current artemisinin derivatives and emergence of multidrug resistance for artemisinin based combination therapies[24] are the motivation to search for novel artemisinin compounds for anti-viral propperties.

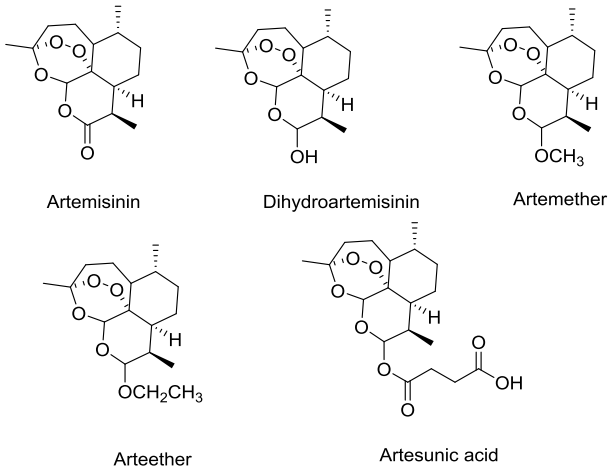


Figure 10 Structures of artemisinin and its semi -synthetic derivatives

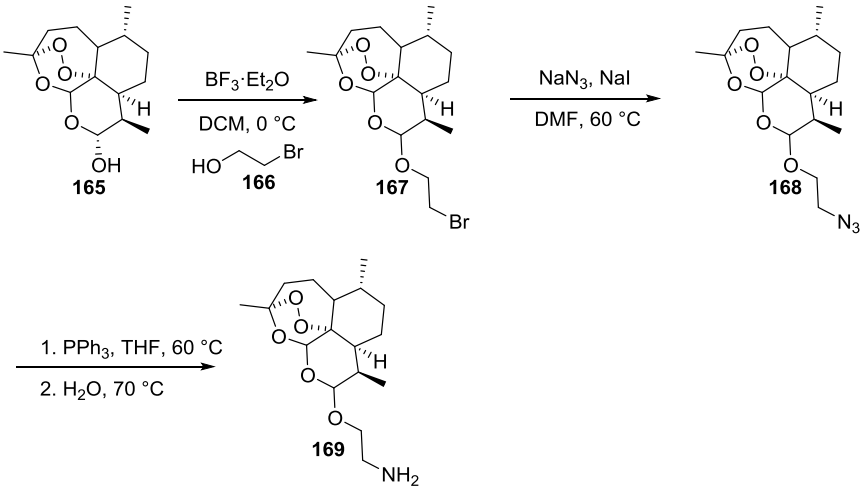
Although 1,2,3-triazole derivatives of artemisinin have been synthesized and evaluated for biological activity,[25, 26] no attempt has been made to synthesize 1,5-disubstituted 1,2,3-triazole derivatives of dihydroartemisinin in a single step and metal free conditions. The widespread applications of 1,2,3-triazoles have triggered the demand for metal free and easier access to this privileged scaffold. Herein we disclose the implementation of our recently developed triazolization strategy[27-29] in which dihydroartemisinin scaffold was joined with variety of interesting heterocyclic moieties. We presume that this strategy could help in synthesizing a series of compound with minimal effort to obtain various fused and 1,5-disubstituted triazole derivatives of dihydroartemisinin.

6.2 Results and Discussion

6.2.1 Organocatalytic synthesis of triazole functionalized artemisinin

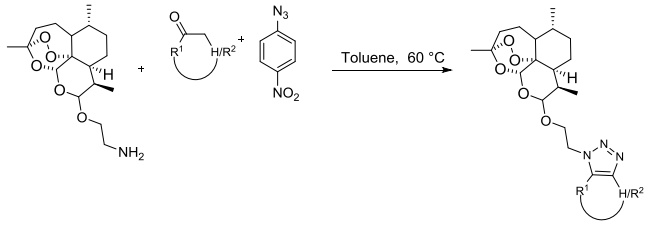
As an effective method of functionalizing dihydroartemisinin with a triazole heterocycle, we implemented our recently developed triazolization strategy.[27–29] The method generally involves the reaction of a primary amine and an enolizable ketone **129** in the presence of 4-nitrophenyl azide **131a** as a source of dinitrogen. The mechanistic

study of this reaction indicated that an equilibrium exists between imine and enamine followed by an enamine mediated [3 + 2] cycloaddition reaction. This leads to the formation of a triazole intermediate followed by elimination of nitroaniline which gave the fused or 1,5-disubstituted 1,2,3-triazole derivative of dihydroartemisinin. It would be interesting to investigate if a delicate structure like dihydroartemisinin could survive the triazolization condition.

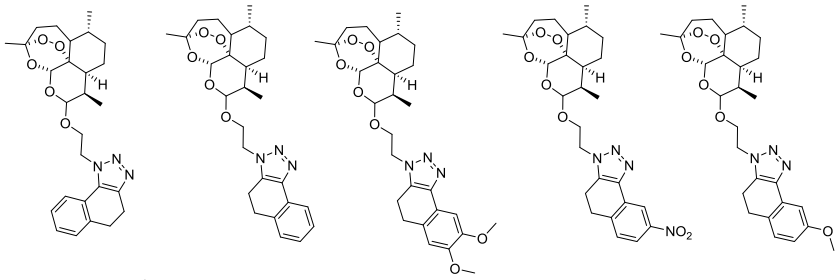


Scheme 40 synthetic route towards the preparation of amine precursor **169**

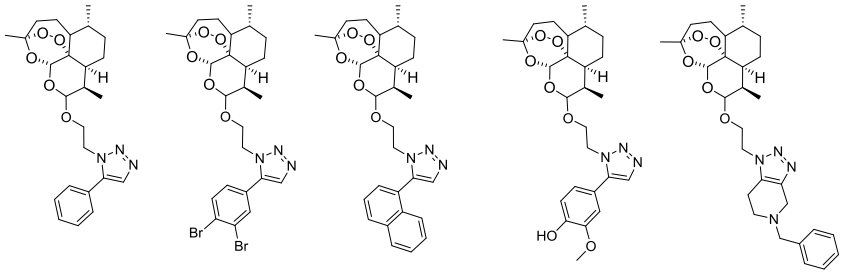
Initially, the amine functionalized dihydroartemisinin **169** was synthesized by a previously reported procedure.[31] It involves the conversion of dihydroartemisinin into 10-bromoethoxydihydroartemisinin **167** by using 2-bromoethanol **166** in the presence of $BF_3{\cdot}Et_2O$ as a catalyst. Reaction of sodium azide with 10-bromoethoxydihydroartemisinin **167** afforded 2-(10b-dihydroartemisinoxy) ethyl azide **168** in isolated yield of 95%. The azido compound was then reduced to 2-(10b-dihydroartemisinoxy) ethyl amine **169** via Staudinger reduction in a yield of 74% (Scheme 40).



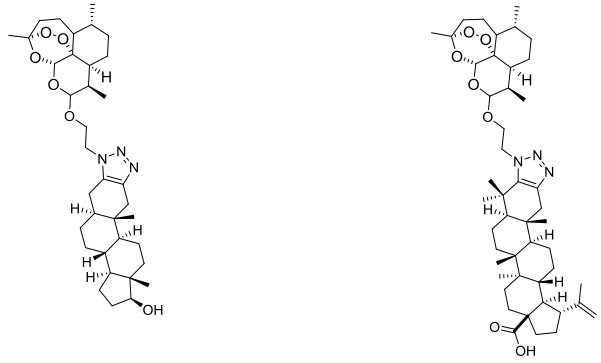
169 **129** **131a** **170**



170a (48%)[b] **170b** (70%) **170c (67%)** **170d** (73%) **170e (66%)**



170f (49%)[b] **170g** (37%)[b] **170h** (53%)[b] **170i** (38%)[b] **170j** (63%)



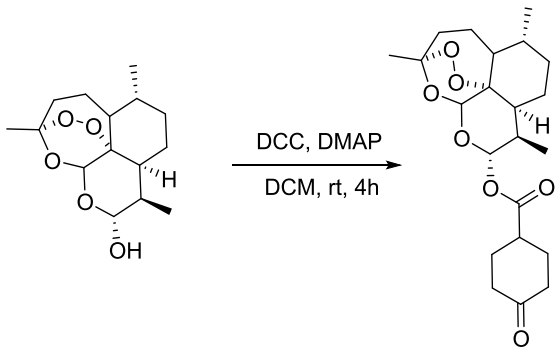
170k (63%) **170l** (47%)

Table 12 substrate scope with respect to ketones [a]

[a]Reaction conditions: **169** (1.0 equiv.), **129** (1.0 equiv.), **131a** (1.2 equiv.), toluene (0.4 mL), 60 °C, 16 h, isolated yield. [b]24 h

The amine modified dihydroartemisinin was then tested for the triazolization strategy with various aromatic and enolizable ketones. Cyclic ketones such as tetralones and their derivatives reacted smoothly under the modified triazolization conditions leading to the expected product in moderate yield. Acetophenone was also converted to the desired product **170f** (Table 12). Next, the versatility of this triazolization reaction was shown by functionalizing the modified dihydroartemisinin **169** with the male sex hormone analogue dihydrotestosterone and the triterpene betulonic acid giving rise to the fused triazole derivatives (**170k** and **170l,** respectively) in moderate yield (Table 12).

In the next series of experiments, we reversed the strategy by functionalizing dihydroatemisinin scaffold with symmetrical enolizable cyclic ketone. The building block **171** was obtained by classical DCC coupling reaction of dihydroartemisinin with cyclohexanone-4-carboxylic acid isolated in 82 % yield (Scheme 36).

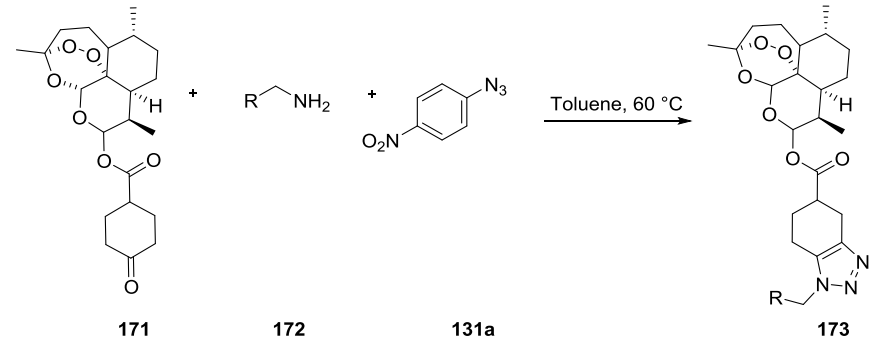


165 **171**

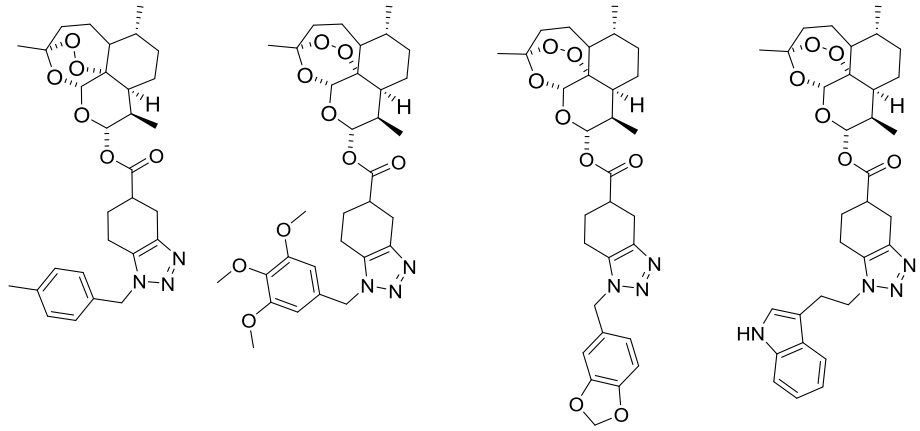
Scheme 41 synthetic route towards the preparation of keto precursor **171**

The versatility of our triazolization methodology was further exploited by condensing with various commercial and biologically relevant primary amine derivatives. Ketone modified dihydroartemisinin **171** was treated with various benzylamines **172** which led to the synthesis of triazole conjugate **173a – 173d** in good yield (Table 13). Tryptamine also works fine under these reaction

circumstances leading to the expected product **173d** in moderate yield (Table 13).



171 **172** **131a** **173**



173a (67%) **173b** (63%) **173c** (61%) **173d** (46%)

Table 13 substrate scope with respect to amines [a]

[a]Reaction conditions: **171** (1.0 equiv.), **172** (1.0 equiv.), **131a** (1.2 equiv.), toluene (0.4 mL), 60 °C, 16 h, isolated yield.

6.2.2 Anti HIV activity evaluation

The newly synthesized dihydroartemisinin triazole derivatives were evaluated for their inhibitory effects (IC_{50}) on the replication of wild-type HIV-1 (III_B) and HIV-2 (ROD) in MT-4 cell cultures, in parallel with their cytotoxicities (CC_{50}) using the 3-(4,5-dimethylthiazol-2-yl)-

2,5-diphenyl tetrazolium bromide (MTT) method.[31] A series of nucleoside reverse transcriptase inhibitors (NRTIs) i.e. azidothymidine (AZT), lamivudine (3TC) and didanosine (DDI), and non-nucleoside reverse transcriptase inhibitors (NNRTIs) i.e. nevirapine (NVP), efavirenz (EFV), and etravirine (ETR) were included as reference compounds. The biological results are represented as IC_{50} and CC_{50} values in Table 14.

Most of the new triazole analogues of dihydroartemisinin are completely devoid of anti-HIV activity. However, the unsubstituted beta-2- tetralone analogue **170b** exhibited moderate activity against wild type HIV-1 III_B with IC_{50} value of 2.78 μM, whereas its alpha tetralone analogue **170a** did not show any activity. Both mono and di-methoxy analogue of beta-tetralone, **170e** and **170c** respectively, are slightly less active against HIV-1 wt with IC_{50} values of 5.18 and 4.06 μM respectively. The active molecules were also evaluated for their inhibitory activity against a double RT mutant (K103N; Y181C) HIV-1 strain (RES056). The derivatives **170b**, **170c** and **170e**, just like the first generation NNRTI nevirapine, completely lose their inhibitory activity, whereas the anti-HIV of efavirenz and etravirine is only slightly affected. Therefore, the active beta-tetralone most probably act via an NNRTI-type mode of action.

Compound	IC_{50} (μM)[a]			CC_{50} (μM)[b]
	HIV-1 strain III_B	HIV-2 strain ROD	HIV-1 strain RES056	
170a	>10.3	>10.3	NT	>10.3
170b	2.78	> 31.5	> 31.5	31.5
170c	4.06	>21.2	>21.2	21.2
170e	5.18	>14.9	>14.9	14.9
azidothymidine	0.0064	0.0082	0.0071	>7.50
lamivudine	2.53	9.90	NT	>87.2
didanosine	76.0	82.1	NT	>212
nevirapine	0.075	>15.0	>15.0	>15.0
efavirenz	0.0024	>6.3	0.18	>6.3
etravirine	0.0034	>2.29	0.045	2.29

Table 14 *In vitro* anti HIV activity and cytotoxicity of triazole derivatives of dihydroartemisinin

[a]IC_{50}: concentration of compound required to achieve 50% protection of MT-4 cell cultures against HIV-1-induced cytotoxicity, as determined by the MTT method.
[b] CC_{50}: concentration required to reduce the viability of mock-infected cell cultures by 50%, as determined by the MTT method.

6.3 Conclusions

In conclusion, a series of newly functionalized artemisinin has been prepared by using a organocatalytic multicomponent reaction. The starting precursors **176** and **178** were used for triazolisation reaction resulting in formation of fused and 1,5-disubstituted 1,2,3-triazole derivatives. All derivatives were screened against HIV wt and three molecules exhibited moderate activity. The beta-tetralone derivatives **170b**, **170c**, and **170e** were inhibitory to HIV-1 replication in cell culture with a limited cytotoxicity. However, no inhibitory activity was observed against HIV-2 and an NNRTI-resitant double RT mutant (K103N; Y181C) HIV-1 strain (RES056), pointing at an NNRTI-type mode of action for the active derivatives. Further studies on modification of artemisinin by triazolization reaction are under investigation and will be reported in due time.

6.4 Experimental section

6.4.1 General procedure for modified triazolization reaction

A flame-dried screw-capped reaction tube equipped with magnetic stirring bar was charged with amine, ketone, 4-nitrophenylazide, and 4 Å molecular sieves. The mixture was dissolved in toluene (0.4 mL) and stirred at 60 °C for 18-36 h. The reaction was monitored by TLC and after completion of reaction, the solvent was removed in *vacuo*. The crude reaction mixture was then subsequently purified by column chromatography (silica gel) first using DCM as eluent to remove all 4-

nitroaniline formed during the reaction, followed by a mixture of heptane and ethyl acetate as the eluent to afford the title product.

6.4.2 Characterization data

1-(2-(((3R,6R,8aS,9R,10R,12R,12aR)-3,6,9-Trimethyldecahydro-12*H*-3,12-epoxy[1,2]dioxepino[4,3-i]isochromen-10-yl)oxy)ethyl)-4,5-dihydro-1*H*-naphtho[1,2-d][1,2,3]triazole (170a): 169 (60 mg, 0.18 mmol), 1-tetralone (26.8 mg, 0.18 mmol), 4-nitrophenylazide (36.1 mg, 0.22 mmol). Reaction time is 24 h. The product was purified by flash column chromatography (at first DCM followed by EtOAc/heptane = 3:2) afforded **170a** (42 mg, 48%) as an off-white semisolid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 7.4 Hz, 1H), 7.30 (td, *J* = 7.4, 1.8 Hz, 1H), 7.24 – 7.17 (m, 2H), 5.38 (s, 1H), 4.62 (d, *J* = 8.0 Hz, 1H), 4.60 – 4.54 (m, 1H), 4.53 – 4.44 (m, 1H), 4.23 (dt, *J* = 10.6, 4.3 Hz, 1H), 3.91 (ddd, *J* = 10.7, 8.6, 4.0 Hz, 1H), 3.09 – 2.91 (m, 4H), 1.87 – 1.81 (m, 1H), 1.71 – 1.62 (m, 3H), 1.60 – 1.49 (m, 3H), 1.47 (s, 3H), 1.44 – 1.35 (m, 1H), 1.29 (dt, *J* = 14.4, 3.2 Hz, 1H), 1.22 – 1.09 (m, 2H), 1.06 – 0.95 (m, 1H), 0.88 (dd, *J* = 6.3, 3.6 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.34, 134.03, 133.69, 129.04, 128.19, 127.37, 127.35, 122.16, 107.27, 101.43, 97.25, 82.73, 68.54, 48.50, 45.24, 44.11, 39.98, 35.27, 34.55, 34.52, 32.81, 28.81, 23.87, 22.17, 19.41, 19.34, 18.76.

3-(2-(((3R,6R,8aS,9R,10R,12R,12aR)-3,6,9-Trimethyldecahydro-12*H*-3,12-epoxy[1,2]dioxepino[4,3-i]isochromen-10-yl)oxy)ethyl)-4,5-dihydro-3*H*-naphtho[1,2-d][1,2,3]triazole (170b): 169 (60 mg, 0.18 mmol), beta-tetralone (26.8 mg, 0.18 mmol), 4-nitrophenylazide (36.1 mg, 0.22 mmol). Reaction time was 16 h. The product was purified by flash column chromatography (at first DCM followed by EtOAc/heptane = 3:2) afforded **170b** (62 mg, 70%) as an off-white solid: mp 104 – 105 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 7.4 Hz, 1H), 7.30 (td, *J* = 7.4, 1.8 Hz, 1H), 7.24 – 7.17 (m, 2H), 5.38 (s, 1H), 4.62 (d, *J* = 8.0 Hz, 1H), 4.60 – 4.54 (m, 1H), 4.53 – 4.44 (m, 1H), 4.23 (dt, *J* = 10.6, 4.3 Hz, 1H), 3.91 (ddd, *J* = 10.7, 8.6, 4.0 Hz, 1H), 3.09 – 2.91 (m, 4H), 1.87 – 1.81 (m, 1H), 1.71 – 1.62 (m, 3H), 1.60 – 1.49 (m, 3H), 1.47 (s, 3H), 1.44 – 1.35 (m, 1H), 1.29 (dt, *J* = 14.4, 3.2 Hz, 1H), 1.22 – 1.09

(m, 2H), 1.06 – 0.95 (m, 1H), 0.88 (dd, *J* = 6.3, 3.6 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.34, 134.03, 133.69, 129.04, 128.19, 127.37, 127.35, 122.16, 107.27, 101.43, 97.25, 82.73, 68.54, 48.50, 45.24, 44.11, 39.98, 35.27, 34.55, 34.52, 32.81, 28.81, 23.87, 22.17, 19.41, 19.34, 18.76.

7,8-Dimethoxy-3-(2-(((3R,6R,8aS,9R,10R,12R,12aR)-3,6,9-trimethyldecahydro-12*H*-3,12-epoxy[1,2]dioxepino[4,3-i]isochromen-10-yl)oxy)ethyl)-4,5-dihydro-3*H*-naphtho[1,2-d][1,2,3]triazole (170c): 169 (60 mg, 0.18 mmol), 6,7-dimethoxy-3,4-dihydronaphthalen-2(1H)-one (37.8 mg, 0.18 mmol), 4-nitrophenylazide (36.1 mg, 0.22 mmol). Reaction time was 16 h. The product was purified by flash column chromatography (at first DCM followed by EtOAc/heptane = 3:2) afforded **170c** (67 mg, 67%) as an off-white semisolid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (s, 1H), 6.76 (s, 1H), 5.38 (s, 1H), 4.62 (d, *J* = 7.9 Hz, 1H), 4.59 – 4.53 (m, 1H), 4.51 – 4.44 (m, 1H), 4.26 – 4.18 (m, 1H), 3.95 (s, 3H), 3.89 (s, 4H), 3.05 – 2.84 (m, 4H), 1.88 – 1.79 (m, 1H), 1.71 – 1.62 (m, 3H), 1.60 – 1.50 (m, 3H), 1.47 (s, 3H), 1.44 – 1.35 (m, 1H), 1.33 – 1.23 (m, 2H), 1.21 – 1.10 (m, 1H), 1.08 – 0.95 (m, 1H), 0.91 – 0.85 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.40, 148.20, 143.46, 133.09, 125.92, 121.85, 111.89, 107.25, 105.67, 101.41, 97.24, 82.71, 68.50, 56.26, 56.18, 48.52, 45.23, 44.12, 39.97, 35.26, 34.55, 34.51, 32.80, 28.45, 23.85, 22.16, 19.62, 19.32, 18.74.

8-Nitro-3-(2-(((3R,6R,8aS,9R,10R,12R,12aR)-3,6,9-trimethyldecahydro-12*H*-3,12-epoxy[1,2]dioxepino[4,3-i]isochromen-10-yl)oxy)ethyl)-4,5-dihydro-3*H*-naphtho[1,2-d][1,2,3]triazole (170d): **169** (60 mg, 0.18 mmol), 7-nitro-3,4-dihydronaphthalen-2(1H)-one (35 mg, 0.18 mmol), 4-nitrophenylazide (36.1 mg, 0.22 mmol). Reaction time was 16 h. The product was purified by flash column chromatography (at first DCM followed by EtOAc/heptane = 3:2) afforded **170d** (70.4 mg 73%) as an off-white semisolid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (d, *J* = 2.2 Hz, 1H), 8.12 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.48 (d, *J* = 8.4 Hz, 1H), 5.38 (s, 1H), 4.91 – 4.87 (m, 2H), 4.61 (d, *J* = 7.9 Hz, 1H), 4.45 – 4.39 (m, 1H), 4.15 – 4.01 (m, 1H), 3.15 – 3.02 (m, 4H), 1.86 – 1.79 (m, 1H), 1.69 – 1.61 (m, 3H), 1.55 –

1.48 (m, 3H), 1.44 (s, 3H), 1.36 – 1.32 (m, 1H), 1.32 – 1.27 (m, 2H), 1.21 – 1.11 (m, 1H), 1.02 – 0.92 (m, 1H), 0.88 – 0.76 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.43, 145.81, 144.66, 131.02, 129.79, 126.95, 123.16, 118.31, 107.19, 101.28, 97.24, 82.76, 77.16, 68.37, 50.36, 45.28, 44.08, 39.56, 35.21, 34.58, 34.51, 32.61, 30.78, 29.85, 23.85, 22.17, 20.38, 19.18, 18.80.

8-Methoxy-3-(2-(((3R,6R,8aS,9R,10R,12R,12aR)-3,6,9-trimethyldecahydro-12*H*-3,12-epoxy[1,2]dioxepino[4,3-i]isochromen-10-yl)oxy)ethyl)-4,5-dihydro-3*H*-naphtho[1,2-d][1,2,3]triazole (170e): 169 (60 mg, 0.18 mmol), 7-methoxy-3,4-dihydronaphthalen-2(1H)-one (32.3 mg, 0.18 mmol), 4-nitrophenylazide (36.1 mg, 0.22 mmol). Reaction time is 16 h. The product was purified by flash column chromatography (at first DCM followed by EtOAc/heptane = 3:2) afforded **170e** (62 mg 66%) as an off-white semisolid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 2.7 Hz, 1H), 7.13 (d, *J* = 8.3 Hz, 1H), 6.75 (dd, *J* = 8.3, 2.7 Hz, 1H), 5.37 (s, 1H), 4.62 (d, *J* = 8.0 Hz, 1H), 4.60 – 4.54 (m, 1H), 4.53 – 4.45 (m, 1H), 4.27 – 4.19 (m, 1H), 3.95 – 3.88 (m, 1H), 3.86 (s, 3H), 3.04 – 2.88 (m, 4H), 1.86 – 1.80 (m, 1H), 1.71 – 1.62 (m, 3H), 1.61 – 1.49 (m, 3H), 1.47 (s, 3H), 1.43 – 1.35 (m, 1H), 1.34 – 1.27 (m, 2H), 1.22 – 1.15 (m, 1H), 1.06 – 0.95 (m, 1H), 0.90 – 0.86 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.10, 143.39, 134.39, 129.97, 129.15, 125.68, 113.95, 107.26, 106.62, 101.41, 97.23, 82.71, 68.49, 55.62, 48.52, 45.22, 44.10, 39.95, 35.25, 34.54, 34.50, 32.79, 27.96, 23.85, 22.15, 19.63, 19.32, 18.74.

5-Phenyl-1-(2-(((3R,6R,8aS,9R,10R,12R,12aR)-3,6,9-trimethyldecahydro-12*H*-3,12-epoxy[1,2]dioxepino[4,3-i]isochromen-10-yl)oxy)ethyl)-1*H*-1,2,3-triazole (170f): 169 (60 mg, 0.18 mmol), acetophenone (22 mg, 0.18 mmol), 4-nitrophenylazide (36.1 mg, 0.22 mmol). Reaction time is 24 h. The product was purified by flash column chromatography (at first DCM followed by EtOAc/heptane = 3:2) afforded **170f** (41 mg 49 %) as an off-white semisolid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.53 – 7.44 (m, 5H), 5.35 (s, 1H), 4.64 – 4.46 (m, 3H), 4.32 – 4.21 (m, 1H), 4.12 – 4.00 (m,

1H), 1.88 – 1.79 (m, 1H), 1.70 – 1.62 (m, 3H), 1.61 – 1.49 (m, 3H), 1.47 (s, 3H), 1.42 – 1.33 (m, 1H), 1.31 – 1.22 (m, 2H), 1.21 – 1.12 (m, 1H), 1.06 – 0.94 (m, 1H), 0.89 – 0.81 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.90, 132.92, 129.45, 129.26, 129.10, 127.25, 107.23, 101.60, 97.23, 82.71, 68.08, 48.04, 45.27, 44.12, 39.70, 35.27, 34.57, 34.53, 32.79, 23.86, 22.17, 19.19, 18.76.

5-(3,4-Dibromophenyl)-1-(2-(((3R,6R,8aS,9R,10R,12R,12aR)-3,6,9-trimethyldecahydro-12H-3,12-epoxy[1,2]dioxepino[4,3-i]isochromen-10-yl)oxy)ethyl)-1*H*-1,2,3-triazole (170g): 169 (60 mg, 0.18 mmol), 1-(3,4-dibromophenyl)ethan-1-one (51 mg, 0.18 mmol), 4-nitrophenylazide (36.1 mg, 0.22 mmol). Reaction time was 36 h. The product was purified by flash column chromatography (at first DCM followed by EtOAc/heptane = 3:2) afforded **170g** (42 mg 37%) as an off-white solid: mp 105 – 106 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 2.0 Hz, 1H), 7.73 – 7.69 (m, 2H), 7.32 (dd, *J* = 8.3, 2.1 Hz, 1H), 5.31 (s, 1H), 4.60 – 4.52 (m, 3H), 4.28 – 4.22 (m, 1H), 4.07 – 4.00 (m, 1H), 1.86 – 1.80 (m, 1H), 1.71 – 1.64 (m, 2H), 1.62 – 1.56 (m, 3H), 1.54 – 1.49 (m, 1H), 1.46 (s, 3H), 1.32 – 1.22 (m, 3H), 1.19 – 1.10 (m, 2H), 1.04 – 0.95 (m, 1H), 0.88 (d, *J* = 5.7 Hz, 3H), 0.84 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 134.32, 134.22, 133.20, 129.19, 128.04, 126.35, 125.68, 107.26, 101.58, 97.21, 82.71, 68.42, 48.52, 45.24, 44.09, 39.71, 35.27, 34.56, 34.53, 32.81, 23.87, 22.17, 19.22, 18.78.

5-(Naphthalen-1-yl)-1-(2-(((3R,6R,8aS,9R,10R,12R,12aR)-3,6,9-trimethyldecahydro-12*H*-3,12-epoxy[1,2]dioxepino[4,3-i]isochromen-10-yl)oxy)ethyl)-1*H*-1,2,3-triazole (170h): 169 (60 mg, 0.18 mmol), 1-(naphthalen-1-yl)ethan-1-one (31.2 mg, 0.18 mmol), 4-nitrophenylazide (36.1 mg, 0.22 mmol). Reaction time was 36 h. The product was purified by flash column chromatography (at first DCM followed by EtOAc/heptane = 3:2) afforded **170h** (49 mg 53%) as an off-white semisolid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.2 Hz, 1H), 7.92 (d, *J* = 7.7 Hz, 1H), 7.79 (s, 1H), 7.58 – 7.46 (m, 5H), 5.24 (s, 1H), 4.51 (d, *J* = 8.0 Hz, 1H), 4.42 – 4.34 (m, 2H), 4.13 – 4.04 (m, 1H), 3.92 – 3.83 (m, 1H), 1.84 – 1.78 (m, 1H), 1.72 – 1.58 (m, 3H), 1.57 – 1.45 (m,

3H), 1.41 (s, 3H), 1.31 – 1.23 (m, 1H), 1.19 – 1.09 (m, 3H), 1.01 – 0.93 (m, 1H), 0.89 – 0.80 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.53, 134.52, 133.76, 132.25, 130.29, 129.05, 128.66, 127.34, 126.66, 125.27, 125.00, 124.59, 107.13, 101.35, 97.16, 82.65, 67.70, 48.24, 45.26, 44.05, 39.52, 35.23, 34.56, 34.52, 32.70, 23.83, 22.15, 19.25, 18.76.

2-Methoxy-4-(1-(2-(((3R,6R,8aS,9R,10R,12R,12aR)-3,6,9-trimethyldecahydro-12*H*-3,12-epoxy[1,2]dioxepino[4,3-i]isochromen-10-yl)oxy)ethyl)-1*H*-1,2,3-triazol-5-yl)phenol (170i): 169 (60 mg, 0.18 mmol), 1-(4-hydroxy-3-methoxyphenyl)ethan-1-one (30.5 mg, 0.18 mmol), 4-nitrophenylazide (36.1 mg, 0.22 mmol). Reaction time was 36 h. The product was purified by flash column chromatography (at first DCM followed by EtOAc/heptane = 3:2) afforded **170i** (35 mg 38%) as an off-white semisolid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.01 (s, 3H), 5.86 (s, 1H), 5.34 (s, 1H), 4.59 (d, *J* = 7.9 Hz, 1H), 4.57 – 4.44 (m, 2H), 4.31 – 4.21 (m, 1H), 4.11 – 4.02 (m, 1H), 3.93 (s, 3H), 1.88 – 1.80 (m, 1H), 1.70 – 1.58 (m, 3H), 1.57 – 1.50 (m, 3H), 1.47 (s, 3H), 1.40 – 1.31 (m, 1H), 1.30 – 1.20 (m, 2H), 1.18 – 1.10 (m, 1H), 1.06 – 0.96 (m, 1H), 0.89 – 0.81 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.91, 138.98, 132.62, 122.83, 118.92, 115.07, 111.85, 107.27, 101.57, 97.25, 82.69, 68.20, 56.29, 47.85, 45.25, 44.10, 39.83, 35.27, 34.56, 34.53, 32.81, 29.84, 23.84, 22.17, 19.19, 18.77.

5-Benzyl-1-(2-(((3R,6R,8aS,9R,10R,12R,12aR)-3,6,9-trimethyldecahydro-12*H*-3,12-epoxy[1,2]dioxepino[4,3-i]isochromen-10-yl)oxy)ethyl)-4,5,6,7-tetrahydro-1*H*-[1,2,3]triazolo[4,5-c]pyridine (170j): 169 (60 mg, 0.18 mmol), 1-benzylpiperidin-4-one (34.7 mg, 0.18 mmol), 4-nitrophenylazide (36.1 mg, 0.22 mmol). Reaction time was 16 h. The product was purified by flash column chromatography (at first DCM followed by EtOAc/heptane = 3:2) afforded **170j** (61 mg 63%) as an off-white semisolid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.28 (m, 5H), 5.37 (s, 1H), 4.60 (d, *J* = 7.9 Hz, 1H), 4.52 - 4,46 (m, 1H), 4.42 – 4.34 (m, 1H), 4.23 – 4.17 (m, 1H), 3.90 – 3.82 (m, 1H), 3.75 (s, 2H), 3.72 – 3.64 (m, 2H), 2.85

- 2,68 (m, 4H), 1.85 – 1.81 (m, 1H), 1.70 – 1.53 (m, 6H), 1.47 (s, 3H), 1.39 - 1.36 (m, 1H), 1.34 – 1.26 (m, 1H), 1.95 - 1.12 (m, 2H), 1.08 – 0.99 (m, 1H), 0.92 - 0.83 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.03, 138.18, 131.76, 129.08, 128.52, 127.46, 107.26, 101.43, 97.23, 82.71, 68.54, 61.64, 49.92, 49.39, 48.23, 45.25, 44.14, 39.93, 35.26, 34.55, 34.52, 32.81, 29.82, 23.86, 22.16, 20.99, 19.28, 18.76.

(**1S,3aS,3bR,5aS,10aS,10bS,12aS)-10a,12a-Dimethyl-7-(2-(((3R,6R,8aS,9R,10R,12R,12aR)-3,6,9-trimethyldecahydro-12H-3,12-epoxy[1,2]dioxepino[4,3-i]isochromen-10-yl)oxy)ethyl)-1,2,3,3a,3b,4,5,5a,6,7,10,10a,10b,11,12,12a-hexadecahydrocyclopenta[7,8]phenanthro[2,3-d][1,2,3]triazol-1-ol (170k): 169** (60 mg, 0.18 mmol), (5S,8R,9S,10S,13S,14S,17S)-17-hydroxy-10,13-dimethylhexadecahydro-3H-cyclopenta[a]phenanthren-3-one (53.2 mg, 0.18 mmol), 4-nitrophenylazide (36.1 mg, 0.22 mmol). Reaction time was 16 h. The product was purified by flash column chromatography (at first DCM followed by EtOAc/heptane = 3:2) afforded **170k** (72 mg 63%) as an off-white solid: mp 96 – 97 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.39 (s, 1H), 4.61 (d, *J* = 7.9 Hz, 1H), 4.48 (dt, *J* = 14.2, 4.2 Hz, 1H), 4.40 – 4.31 (m, 1H), 4.20 (dt, *J* = 8.9, 4.4 Hz, 1H), 3.91 – 3.85 (m, 1H), 3.66 (t, *J* = 8.5 Hz, 1H), 2.85 (d, *J* = 15.3 Hz, 1H), 2.55 (dd, *J* = 16.2, 5.0 Hz, 1H), 2.30 (t, *J* = 13.6 Hz, 2H), 2.11 – 2.03 (m, 1H), 1.89 - 1.82 (m, 2H), 1.75 – 1.51 (m, 10H), 1.48 – 1.47 (m, 3H), 1.45 – 1.38 (m, 3H), 1.32 – 1.25 (m, 3H), 1.20 – 1.12 (m, 3H), 1.05 – 0.96 (m, 2H), 0.91 – 0.87 (m, 6H), 0.76 (s, 3H), 0.72 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 142.96, 131.85, 107.28, 101.25, 97.27, 82.74, 81.99, 68.40, 53.86, 50.95, 48.03, 45.26, 44.14, 43.00, 42.39, 39.98, 36.96, 36.78, 36.31, 35.75, 35.32, 34.56, 34.54, 32.84, 31.34, 30.60, 29.05, 25.01, 23.87, 23.58, 22.18, 20.93, 19.39, 18.78, 11.73, 11.17.

(1R,3aS,5aR,5bR,7aR,12aR,12bR,14aR,14bR)-5a,5b,8,8,12a-Pentamethyl-1-(prop-1-en-2-yl)-9-(2-(((3R,6R,8aS,9R,10R,12R,12aR)-3,6,9-trimethyldecahydro-12H-3,12-epoxy[1,2]dioxepino[4,3-i]isochromen-10-yl)oxy)ethyl)-

2,3,4,5,5a,5b,6,7,7a,8,9,12,12a,12b,13,14,14a,14b-octadecahydrocyclopenta[7,8]chryseno[2,3-d][1,2,3]triazole-3a(1*H*)-carboxylic acid (170l): 169 (60 mg, 0.18 mmol), (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-9-oxo-1-(prop-1-en-2-yl)icosahydro-3aH-cyclopenta[a]chrysene-3a-carboxylic acid (83 mg, 0.18 mmol), 4-nitrophenylazide (36.1 mg, 0.22 mmol). Reaction time was 16 h. The product was purified by flash column chromatography (at first DCM followed by EtOAc/heptane = 3:2) afforded **170l** (68 mg 47%) as an off-white semisolid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.39 (s, 1H), 4.76 (s, 1H), 4.69 – 4.63 (m, 2H), 4.59 – 4.51 (m, 1H), 4.28 - 4.23 (m, 1H), 4.19 – 4.11 (m, 1H), 3.06 - 3.00 (m, 1H), 2.91 (d, *J* = 15.3 Hz, 1H), 2.31 – 2.23 (m, 2H), 2.12 (d, *J* = 15.3 Hz, 1H), 2.03 – 1.96 (m, 2H), 1.86 – 1.76 (m, 3H), 1.71 (s, 3H), 1.69 – 1.63 (m, 3H), 1.60 – 1.50 (m, 8H), 1.48 (s, 5H), 1.45 – 1.39 (m, 2H), 1.37 (d, *J* = 2.5 Hz, 1H), 1.32 (d, *J* = 7.6 Hz, 4H), 1.29 – 1.22 (m, 9H), 1.18 – 1.10 (m, 3H), 1.00 (d, *J* = 4.6 Hz, 6H), 0.90 - 0.87 (m, 6H), 0.78 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.60, 150.37, 141.10, 138.35, 110.01, 107.26, 101.71, 97.31, 82.75, 68.55, 56.48, 54.86, 49.47, 49.31, 49.21, 47.00, 45.30, 44.10, 42.61, 40.75, 39.80, 39.09, 38.59, 38.42, 37.18, 35.29, 34.60, 34.56, 33.76, 33.54, 32.82, 32.22, 30.71, 29.94, 29.84, 28.82, 25.65, 23.90, 22.19, 21.57, 19.55, 19.33, 19.09, 18.80, 16.17, 15.80, 14.83.

(3R,6R,8aS,9R,12R,12aR)-3,6,9-Trimethyldecahydro-12*H*-3,12-epoxy[1,2]dioxepino[4,3-i]isochromen-10-yl 4-oxocyclohexane-1-carboxylate (171): dihydroartemisinin (1gm, 3.52 mmol), dicyclohexylmethanediimine (0.726 gm, 3.52 mmol), 4-oxocyclohexane-1-carboxylic acid (0.600 gm, 4.22 mmol), *N*,*N*-dimethylpyridin-4-amine (0.064 gm, 0.52 mmol). Reaction time was 18 h. The product is purified by flash column chromatography (DCM/MeOH = 99/1). Afforded **178** (1.2 gm, 84%)as an off-white semisolid:^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82 (d, *J* = 9.8 Hz, 1H), 5.45 (s, 1H), 2.91 – 2.75 (m, 1H), 2.60 (ddd, *J* = 9.9, 7.2, 4.6 Hz, 1H), 2.62 - 2.58 (m, 1H), 2.55 - 2.45 (m, 1H), 2.39 – 2.34 (m, 2H), 2.33 – 2.27 (m, 1H), 2.25 – 2.20 (m, 1H), 2.14 – 2.00 (m, 3H), 1.95 – 1.87 (m, 1H), 1.81 - 1.75 (m, 2H), 1.67 - 1.56 (m, 2H), 1.52 – 1.46 (m, 1H), 1.45 – 1.41 (m, 3H),

1.39 – 1.25 (m, 3H), 1.11 – 1.00 (m, 1H), 0.97 (d, *J* = 6.0 Hz, 3H), 0.86 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 210.13, 173.04, 104.63, 92.27, 91.67, 80.25, 77.48, 76.84, 51.70, 45.39, 40.70, 39.87, 39.66, 37.41, 36.33, 34.21, 31.94, 28.78, 28.05, 26.06, 24.71, 22.13, 20.34, 12.30.

(3R,6R,8aS,9R,10S,12R,12aR)-3,6,9-Trimethyldecahydro-12H-3,12-epoxy[1,2]dioxepino[4,3-i]isochromen-10-yl 1-(4-methylbenzyl)-4,5,6,7-tetrahydro-1*H*-benzo[d][1,2,3]triazole-5-carboxylate (173a): **171** (60 mg, 0.15 mmol), p-tolylmethanamine (18 mg, 0.15 mmol), 4-nitrophenylazide (28.9 mg, 0.18 mmol). Reaction time was 16 h. The product was purified by flash column chromatography (at first DCM followed by EtOAc/heptane = 3:2) afforded **173a** (53 mg, 67%) as an off-white semisolid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (d, *J* = 7.8 Hz, 2H), 7.08 (d, *J* = 7.8 Hz, 2H), 5.83 – 5.69 (m, 1H), 5.48 – 5.29 (m, 3H), 3.20 – 3.05 (m, 1H), 3.03 – 2.91 (m, 1H), 2.86 – 2.76 (m, 1H), 2.68 – 2.50 (m, 2H), 2.44 – 2.36 (m, H), 2.33 (s, 3H), 2.29 – 2.12 (m, 1H), 2.07 – 1.99 (m, 1H), 1.95 – 1.85 (m, 2H), 1.79 – 1.69 (m, 2H), 1.66 – 1.57 (m, 2H), 1.54 – 1.45 (m, 1H), 1.42 (d, *J* = 1.6 Hz, 3H), 1.38 – 1.25 (m, 3H), 0.96 (d, *J* = 5.8 Hz, 3H), 0.80 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.24, 172.94, 141.10, 141.06, 136.27, 136.21, 132.13, 127.09, 127.02, 122.90, 122.73, 122.40, 122.24, 119.72, 119.63, 118.14, 118.05, 111.69, 111.62, 111.23, 104.76, 104.72, 92.59, 92.53, 91.82, 80.38, 80.22, 51.74, 51.70, 48.99, 48.80, 45.35, 39.53, 39.38, 37.40, 36.38, 34.18, 32.02, 31.90, 26.77, 26.68, 26.03, 25.92, 25.02, 24.80, 24.69, 24.35, 23.84, 22.15, 20.34, 18.23, 18.04, 12.32, 12.22.

(3R,6R,8aS,9R,10S,12R,12aR)-3,6,9-Trimethyldecahydro-12*H*-3,12-epoxy[1,2]dioxepino[4,3-i]isochromen-10-yl 1-(3,4,5-trimethoxybenzyl)-4,5,6,7-tetrahydro-1*H*-benzo[d][1,2,3]triazole-5-carboxylate (173b): **171** (60 mg, 0.15 mmol), (3,4,5-trimethoxyphenyl)methanamine (29 mg, 0.15 mmol), 4-nitrophenyl azide (28.9 mg, 0.18 mmol). Reaction time was 16 h. The product was purified by flash column chromatography (at first DCM followed by EtOAc/heptane = 3:2) afforded **173b** (55 mg, 61%) as an off-white

solid: mp 81 – 80 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.40 (d, *J* = 6.8 Hz, 2H), 5.82 – 5.74 (m, 1H), 5.43 (t, *J* = 4.6 Hz, 1H), 5.39 – 5.28 (m, 2H), 3.83 (d, *J* = 1.0 Hz, 3H), 3.81 (d, *J* = 1.5 Hz, 6H), 3.20 – 2.94 (m, 2H), 2.88 – 2.81 (m, 1H), 2.74 – 2.54 (m, 2H), 2.52 – 2.42 (m, 1H), 2.42 – 2.33 (m, 1H), 2.31 – 2.20 (m, 1H), 2.02 – 1.86 (m, 2H), 1.79 – 1.68 (m, 2H), 1.66 – 1.59 (m, 1H), 1.42 (d, *J* = 3.5 Hz, 3H), 1.32 – 1.23 (m, 4H), 0.97 (d, *J* = 5.8 Hz, 3H), 0.90 – 0.84 (m, 2H), 0.81 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.06, 172.85, 153.77, 142.64, 142.33, 138.12, 131.47, 131.12, 130.33, 130.30, 104.73, 104.66, 104.61, 104.57, 92.30, 91.65, 80.22, 80.20, 60.97, 56.34, 52.31, 52.28, 51.67, 45.37, 45.33, 39.82, 39.47, 37.39, 36.31, 34.18, 31.92, 31.87, 29.81, 26.03, 25.47, 24.99, 24.68, 24.20, 22.09, 20.31, 19.29, 18.87, 12.24, 12.16.

(3R,6R,8aS,9R,10S,12R,12aR)-3,6,9-Trimethyldecahydro-12H-3,12-epoxy[1,2]dioxepino[4,3-i]isochromen-10-yl 1-(benzo[d][1,3]dioxol-5-ylmethyl)-4,5,6,7-tetrahydro-1*H*-benzo[d][1,2,3]triazole-5-carboxylate (173c): 171 (60 mg, 0.15 mmol), benzo[d][1,3]dioxol-5-ylmethanamine (22.2 mg, 0.15 mmol), 4-nitrophenylazide (28.9 mg, 0.18 mmol). Reaction time was 16 h. The product was purified by flash column chromatography (at first DCM followed by EtOAc/heptane = 3:2) afforded **173c** (51 mg, 61%)as an off-white semisolid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76 (dd, *J* = 6.9, 1.7 Hz, 1H), 6.68 (dt, *J* = 3.7, 1.6 Hz, 2H), 5.96 (s, 2H), 5.83 – 5.73 (m, 1H), 5.43 (d, *J* = 3.0 Hz, 1H), 5.39 – 5.25 (m, 2H), 3.18 – 3.06 (m, 1H), 3.04 – 2.92 (m, 1H), 2.87 – 2.78 (m, 1H), 2.69 – 2.54 (m, 2H), 2.47 – 2.33 (m, 2H), 2.28 – 2.19 (m, 1H), 2.06 – 1.86 (m, 3H), 1.79 – 1.69 (m, 2H), 1.66 – 1.58 (m, 1H), 1.51 – 1.45 (m, 1H), 1.42 (d, *J* = 1.9 Hz, 3H), 1.34 – 1.24 (m, 2H), 1.07 – 0.98 (m, 1H), 0.96 (d, *J* = 5.9 Hz, 3H), 0.91 – 0.84 (m, 1H), 0.83 – 0.78 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.09, 172.92, 148.40, 147.87, 142.33, 131.34, 128.43, 121.33, 108.54, 108.21, 108.19, 104.59, 104.55, 101.45, 92.29, 91.64, 80.22, 80.19, 51.98, 51.67, 45.38, 45.33, 39.47, 37.38, 37.36, 36.31, 34.18, 31.92, 31.86, 26.04, 25.50, 24.99, 24.67, 24.23, 22.08, 20.31, 19.36, 18.86, 12.15.

(3R,6R,8aS,9R,10S,12R,12aR)-3,6,9-Trimethyldecahydro-12*H*-3,12-epoxy[1,2]dioxepino[4,3-i]isochromen-10-yl 1-(2-(1*H*-indol-3-yl)ethyl)-4,5,6,7-tetrahydro-1*H*-benzo[d][1,2,3]triazole-5-carboxylate (173d): 171 (60 mg, 0.15 mmol), 2-(1H-indol-3-yl)ethan-1-amine (25.5 mg, 0.15 mmol), 4-nitrophenylazide (28.9 mg, 0.18 mmol). Reaction time was 16 h. The product was purified by flash column chromatography (at first DCM followed by EtOAc/heptane = 3:2) afforded **173d** (39 mg, 46%) as an off-white semisolid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, *J* = 7.1 Hz, 1H), 7.43 – 7.33 (m, 2H), 7.22 – 7.16 (m, 1H), 7.11 – 7.06 (m, 1H), 6.70 (dd, *J* = 51.1, 2.3 Hz, 1H), 5.73 (dd, *J* = 9.9, 6.4 Hz, 1H), 5.47 (d, *J* = 13.4 Hz, 1H), 4.53 – 4.31 (m, 2H), 3.37 – 3.24 (m, 2H), 3.06 – 2.87 (m, 2H), 2.70 – 2.55 (m, 2H), 2.42 – 2.32 (m, 1H), 2.03 (ddd, *J* = 14.5, 7.3, 4.2 Hz, 1H), 1.93 – 1.85 (m, 3H), 1.82 – 1.74 (m, 2H), 1.72 – 1.61 (m, 4H), 1.54 – 1.41 (m, 1H), 1.41 – 1.34 (m, 4H), 1.34 – 1.25 (m, 2H), 0.97 (d, *J* = 5.6 Hz, 3H), 0.83 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.24, 172.94, 141.10, 141.06, 136.27, 136.21, 132.13, 127.09, 127.02, 122.90, 122.73, 122.40, 122.24, 119.72, 119.63, 118.14, 118.05, 111.69, 111.62, 111.23, 104.76, 104.72, 92.59, 92.53, 91.82, 80.38, 80.22, 51.74, 51.70, 48.99, 48.80, 45.35, 39.53, 39.38, 37.40, 36.38, 34.18, 32.02, 31.90, 26.77, 26.68, 26.03, 25.92, 25.02, 24.80, 24.69, 24.35, 23.84, 22.15, 20.34, 18.23, 18.04, 12.32, 12.22.

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Chapter 7
Synthesis and anticancer activity of novel aza-artemisinin derivatives

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Sampad Jana planned the experiments, analyzed the data and wrote the manuscript.

7.1 Introduction

Artemisinin, which is a naturaly occouring 1,2,4-trioxane sesquiterpene, is well known to possess antimalarial activity.[1,2] Artemisinin and its derivatives have shown an excellent safety profile. Recently it has been discovered that artemisinin derivatives also possess anticancer activity with low toxicity.[3-11] Although the mechanism of action is still not clear, one of the believed reasons behind both the anticancer and antimalarial activity is the generation of highly cytotoxic carbon-centred free radicals by reaction of iron ions with the endoperoxyl moiety of artemisinin.[11] In order to increase the therapeutic value, several derivatives of artemisinin have been prepared in recent years.[3-10] However, biodegradation by the liver, and resulting short half life undermine the therapeutic value of artemisinin.[11] Artemisinin derivatives which are devoid of these deficiencies will have a high chance to go into clinical trials. Thus, an urgent investigation is needed to improve the pharmacological properties of artemisinin derivatives.

The applications of the click reaction have grown significantly in various research fields in chemistry, ranging from medicinal chemistry to material chemistry since the discovery by Sharpless and Meldal.[12] Due to the mild reaction conditions and the high functional group tolerance, the click reaction has been used in diverse fields of chemistry for linking two partners via a triazole.[13,14] Beside the click reaction several synthetic strategies have been discovered toward triazoles.[15,16] Recently, the triazolization strategy developed by our group has drawn considerable attention. This metal-free strategy enables the synthesis of various previously inaccessible 1,5-disubstituted and fused 1,2,3-triazole derivatives from commercialy and readily available starting materials such as unactivated enolizable ketones and primary amines.[17-19]

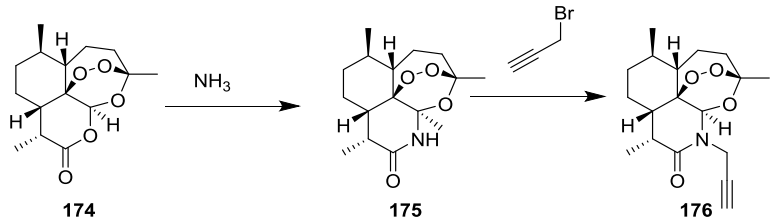
Several heterocyclic derivatives of artemisinin were developed in order to increase the anticancer properties.[3-10] Almost all the modifications were done at the C-10 carbon atom. In contrast, only a limited number of modifications at O-11 were reported.[20] Among these, 11-aza-artemisinin and its derivatives were mostly studied and are known to possess various biological activities. However, the lack of

an efficient functional handle for further diversification of aza-artemisinin limits its application in pharmaceutical chemistry.[21] Hence the development of a synthetic route by which a series of diverse derivatives of artemisinin could be prepared is necessary. Here we would like to disclose the synthesis and anticancer activity of a series of 11-aza-artemisinin derivatives, which were prepared by the general click reactions, as well as dihydroartemisinin derivatives, prepared via triazolization strategies.[22]

7.2 Results and discussions

7.2.1 Chemistry

At first 11-aza-artemisinin **175** has been prepared starting from artemisinin **174** by a previously reported method (Scheme 42)[20]. In accordance to that method, 11-aza-artemisinin **175** was obtained by immersion of artemisinin in liquid ammonia at -15 ˚C. The 11-aza-artemisinin **175** was then treated with propargyl bromide in the presence of a base resulting in the propargyl derivative of 11-aza-artemisinin **176** (scheme 41), which readily undergoes click reaction with various azides to form a library of 1,4-disubstituted triazoles (**177a**-**177g**) in excellent yield (Table 15).



Scheme 42: Synthesis of propargyl derivative of 11-aza-artemisinin

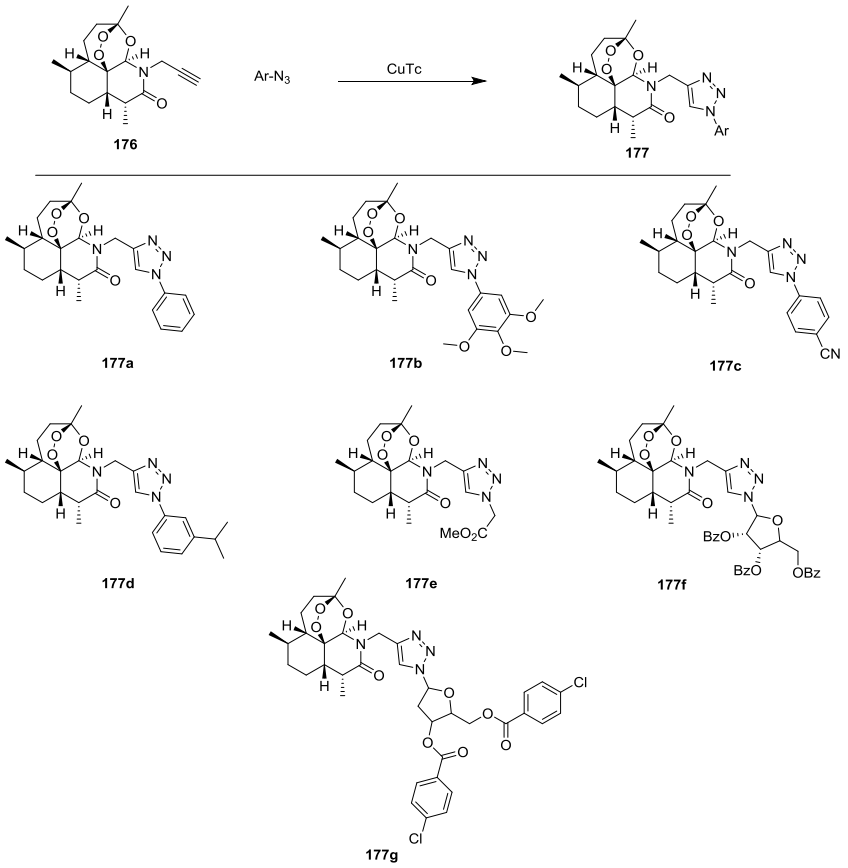


Table 15 List of compounds from click reaction

Next, two series of compounds were prepared via triazolization strategy.[17-19] Out of the total of three series, the second one was based on the variation of ketones and third one was about the variation of amines. In the second strategy, the amine **169** was synthesized in three steps starting from dihydroartemisinin.[22] The amine functionalized dihydroartemisinin **169** was subsequently treated with various enolizable ketones **129** and 4-nitrophenyl azide **131a**, yielding the desired 1,5-disubstituted or fused 1,2,3-triazoles **170a**-**170l** (Table 16). Products from the third stategy were obtained by varying amines. The starting ketone **171** was synthesized from dihydroartemisinin in a one-step fashion. The dihydroartemisinin functionalized ketone was then

treated with amine **172** and 4-nitrophenyl azide, resulting in the formation of fused 1,2,3-triazoles **173a**-**173d** (Table 17).

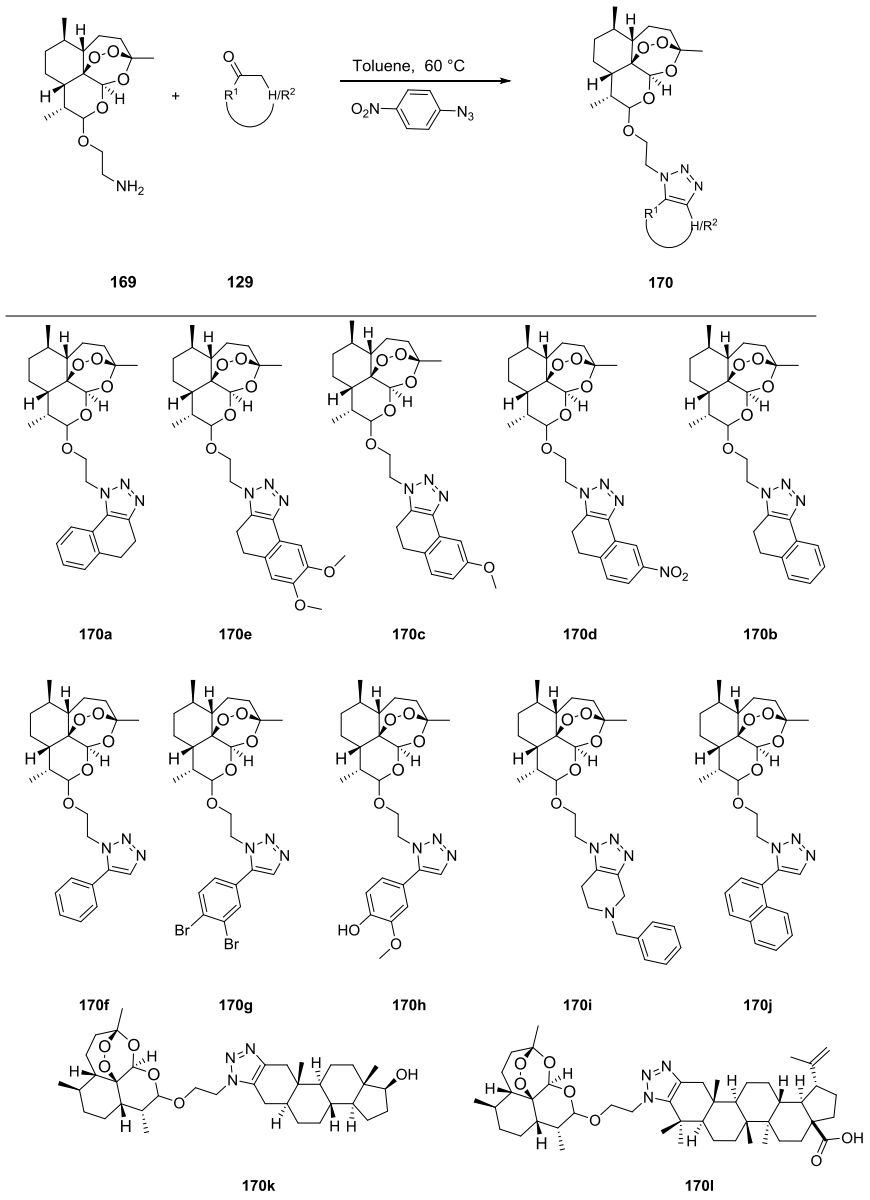


Table 16 Variations of ketones in triazolization reactions

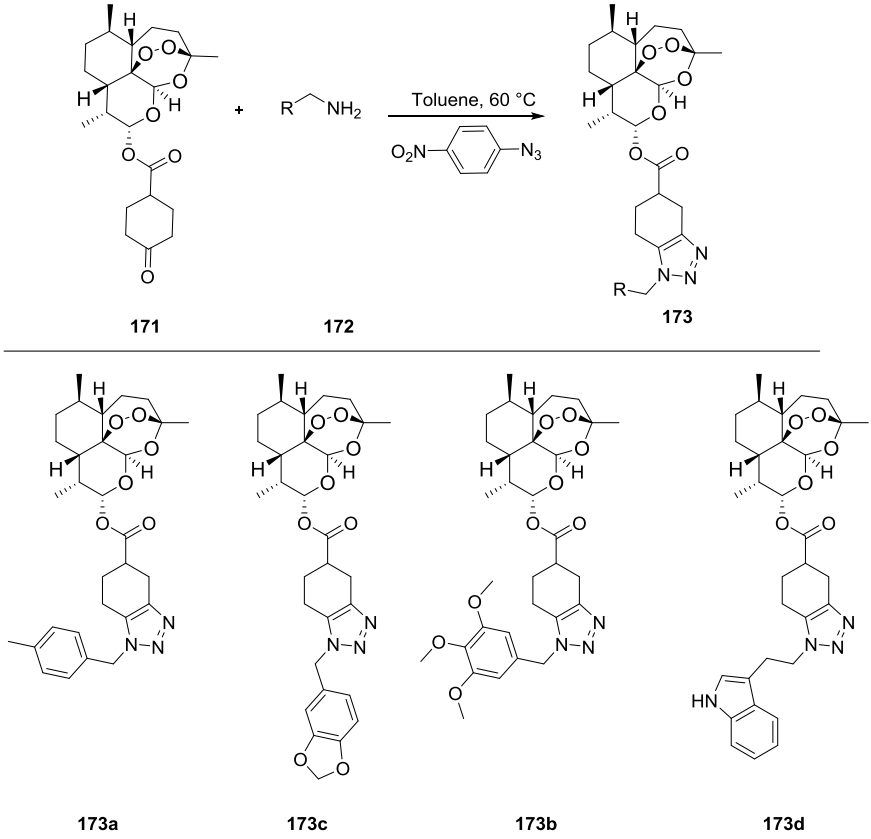


Table 17 Variations of amines in triazolization reaction

7.2.2 Biological activity

The anti-proliferative activity of the synthesized compounds was evaluated in 2 tumor cell lines: human T-lymphoblastic leukemia (CEM) and human cervical carcinoma (HeLa) cells, and in human dermal microvascular endothelial HMEC-1 cells. Data are expressed as IC_{50} (50% inhibitory concentration), which is defined as the compound concentration that reduces cell proliferation by 50%, and are shown in Table 18.

Aza-artemisinin (**175**) did not inhibit the growth of the cell lines tested (IC_{50} >150 µM). Also, its propargyl derivative (**176**) only showed a cytostatic effect at 100 µM. However, several 1,4-disubstituted

triazoles (**177a**-**177d** and **177g**) displayed a marked anti-proliferative activity; the most active compounds being **177d** and **177g**, with IC_{50} values in CEM cells of 0.92 and 2.6 µM, respectively. Notably, compounds **177a**, **177b** and **177d** proved 8- to 50-fold less active in HMEC-1 endothelial cells compared to CEM leukemia cells, which may point to a tumor-selective effect of these compounds.

The 1,5-disubstituted triazoles derived from dihydro-artemisinin (**170a**-**170l**) caused a modest inhibition of cell proliferation ($IC_{50} \geq 10$ µM). Only compounds **170k** and **170l** displayed an anti-proliferative activity below 10 µM in CEM cells. However, low-micromolar cytostatic activity was obtained in cells treated with fused 1,2,3-triazoles (**173a**-**173d**). Interestingly, also these compounds were most active in CEM (IC_{50} of 2-4 µM), compared to HeLa (IC_{50} of 11-21 µM) and endothelial cells (IC_{50} of 34-40 µM).

Name	IC_{50} (µM)		
	CEM	HeLa	HMEC-1
175	150 ± 15	147 ± 11	> 250
176	104 ± 23	98 ± 51	241 ± 12
177a	5.1 ± 0.9	36 ± 1	> 250
177b	17 ± 1	19 ± 4	155 ± 1
177c	18 ± 5	36 ± 21	26 ± 8
177d	0.92 ± 0.24	1.2 ± 0.2	30 ± 0
177e	≥ 250	> 250	> 250
177f	> 250	≥ 250	> 250
177g	2.6 ± 1.0	6.1 ± 0.8	24 ± 8
170a	21 ± 0	20 ± 0	35 ± 6
170b	157 ± 41	> 250	> 250
170c	128 ± 44	143 ± 40	105 ± 107

170d	95 ± 5	175 ± 106	160 ± 1
170e	30 ± 7	36 ± 9	150 ± 3
170f	25 ± 5	37 ± 5	62 ± 11
170g	10 ± 0	11 ± 6	26 ± 0
170h	39 ± 3	23 ± 3	62 ± 41
170i	20 ± 2	19 ± 3	30 ± 0
170j	11 ± 0	12 ± 1	24 ± 1
170k	8.9 ± 3.3	16 ± 9	28 ± 0
170l	5.0 ± 0.3	24 ± 19	121 ± 6
173a	2.7 ± 0.2	11 ± 0	34 ± 0
173b	4.3 ± 0.2	21 ± 4	40 ± 5
173c	2.8 ± 0.2	11 ± 1	35 ± 4
173d	3.9 ± 0.6	12 ± 7	40 ± 0

Table 18 In vitro anticancer activity of triazole derivatives of artemisinin

7.3 Conclusion

In summary, we have developed three synthetic strategies to access 1,4-disubstituted, 1,5-disubstituted, and fused 1,2,3-triazoles analogues of artemisinin with promising anticancer activity. The click reaction allowed regioselective cycloaddition of alkynes and azides resulting in the formation of 1,4-disubstituted 1,2,3-triazoles, whereas the triazolization reaction allowed access to 1,5-disubstituted and fused 1,2,3-triazoles analogues. All the synthesized compounds were tested for their anticancer activity against 2 cancer cell lines and 1 endothelial cell line. The highest activity was found for compound **177d** with IC_{50} values of 0.92 µM and 1.2 µM in CEM and HeLa cells, respectively. Moreover, compound **177d** proved to be 30-fold more active in tumor versus endothelial cells, pointing to a potential tumor-

selective mechanism of action. Considering promising activity of **177d** in cancer cell line, a new series of artemisinin derivatives should be prepared further for their evaluation of anticancer activity.

7.4 Experimental Section

Preparation of propargyl derivative of 11-aza-artemisinin (176)

NaOH (0.138 g, 3.13 mmol) was added to a solution of 11-azaartemisinin (1g, 3.13 mmol) in dry THF (10 mL). The resulting mixture was stirred for 30 minutes at room temperature. Then a solution of propargyl bromide (1.86 g, 15.65 mmol) in dry THF (5 mL) was added dropwise at same temperature. The mixture was then stirred at room temperature for overnight. The completion of reaction was then monitored by TLC. Once the reaction was finished, the solvent was evaporated and the crude mixture was purified by silica gel flash column chromatography (heptane/ethyl acetate = 9:1) to afford the desired product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.45 (s, 1H), 4.81 (dd, J = 17.0, 2.3 Hz, 1H), 3.93 (dd, J = 17.0, 2.0 Hz, 1H), 3.36 – 3.25 (m, 1H), 2.49 – 2.39 (m, 1H), 2.14 (s, 1H), 2.06 – 1.98 (m, 2H), 1.83 – 1.72 (m, 2H), 1.71 – 1.64 (m, 1H), 1.57 – 1.43 (m, 2H), 1.40 – 1.34 (m, 4H), 1.15 (d, J = 7.3 Hz, 3H), 1.06 – 0.97 (m, 4H), 0.97 – 0.85 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.72, 105.01, 80.29, 79.14, 77.40, 70.98, 51.53, 45.88, 37.75, 36.69, 33.85, 33.25, 30.44, 25.41, 25.20, 22.73, 19.88, 12.78. HRMS (ESI+): m/z calcd for $C_{18}H_{25}NO_4$ $[M+H]^+$: 320.1856, found 320.1832.

7.4.1 General procedure for click reaction

A flame-dried reaction tube equipped with magnetic stirring bar was charged with **176**, corresponding azides, and CuTc. The mixture was dissolved in corresponding solvents and stirred at room temperature for overnight. The crude reaction mixture was then dried over vacuum and purified by silica gel flash column chromatography.

7.4.2 Charactarization data

Artemisinin derivative 177a: 176 (100 mg, 0.31 mmol), azidobenzene (44.8 mg, 0.38 mmol), CuTc (5.97 mg, 0.03 mmol). Dry DMF (0.5 mL). Reaction time was 12 h. The product was purified by flash column chromatography (EtOAc/heptane = 1:9) to afford **177a** (108 mg, 79%) as an off-white semi solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.73 (d, *J* = 7.9 Hz, 2H), 7.51 (t, *J* = 7.6 Hz, 2H), 7.41 (t, *J* = 7.3 Hz, 1H), 5.58 (s, 1H), 4.91 – 4.79 (m, 2H), 3.38 – 3.30 (m, 1H), 2.46 – 2.37 (m, 1H), 2.06 – 1.98 (m, 1H), 1.71 – 1.65 (m, 2H), 1.62 – 1.53 (m, 2H), 1.37 – 1.31 (m, 2H), 1.25 (s, 4H), 1.13 (d, *J* = 7.2 Hz, 3H), 0.98 (d, *J* = 6.3 Hz, 4H), 0.90 – 0.77 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.28, 145.74, 137.24, 129.82, 128.72, 121.49, 120.54, 105.11, 80.51, 78.73, 51.53, 45.94, 37.51, 37.14, 36.79, 33.81, 33.31, 29.84, 25.36, 25.16, 22.82, 19.86, 12.89. HRMS (ESI+): m/z calcd for $C_{24}H_{30}N_4O_4$ $[M+H]^+$: 439.2339, found 439.2330.

Artemisinin derivative 177b: 176 (100 mg, 0.31 mmol), 5-azido-1,2,3-trimethoxybenzene (79 mg, 0.38 mmol), CuTc (5.97 mg, 0.03 mmol). Dry THF (0.5 mL). Reaction time was 12 h. The product was purified by flash column chromatography (EtOAc/heptane = 1:9) to afford **177b** (121 mg, 73%) as an off-white semi solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 6.96 (s, 2H), 5.60 (s, 1H), 4.92 – 4.75 (m, 2H), 3.93 (s, 6H), 3.88 (s, 3H), 3.39 – 3.31 (m, 1H), 2.47 – 2.37 (m, 1H), 2.07 – 1.96 (m, 2H), 1.73 – 1.66 (m, 3H), 1.48 – 1.41 (m, 1H), 1.38 – 1.32 (m, 1H), 1.26 (s, 3H), 1.13 (d, *J* = 7.3 Hz, 3H), 0.98 (d, *J* = 6.3 Hz, 3H), 0.90 – 0.80 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.29, 153.99, 145.65, 138.25, 133.09, 121.59, 105.09, 98.25, 80.47, 78.76, 61.16, 56.61, 51.49, 45.91, 37.50, 37.12, 36.76, 33.78, 33.28, 25.35, 25.15, 22.80, 19.83, 12.86. HRMS (ESI+): m/z calcd for $C_{27}H_{36}N_4O_7$ $[M+H]^+$: 529.2656, found 529.2668.

Artemisinin derivative 177c: 176 (100 mg, 0.31 mmol), 4-azidobenzonitrile (54.2 mg, 0.38 mmol), CuTc (5.97 mg, 0.03 mmol). Dry DMF (0.5 mL). Reaction time was 12 h. The product was purified

by flash column chromatography (EtOAc/heptane = 1:9) to afford **177c** (90 mg, 62%) as an off-white semi solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.91 (d, J = 8.8 Hz, 2H), 7.82 (d, J = 8.8 Hz, 2H), 5.56 (s, 1H), 4.83 (q, J = 15.0 Hz, 2H), 3.35 (dd, J = 7.3, 4.6 Hz, 1H), 2.47 – 2.35 (m, 1H), 2.06 – 1.95 (m, 2H), 1.75 – 1.66 (m, 3H), 1.63 (s, 1H), 1.57 – 1.48 (m, 1H), 1.39 – 1.31 (m, 1H), 1.28 – 1.24 (m, 1H), 1.22 (s, 3H), 1.13 (d, J = 7.3 Hz, 3H), 0.99 (d, J = 6.3 Hz, 3H), 0.91 – 0.78 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.38, 146.67, 140.00, 134.00, 121.37, 120.58, 117.90, 112.36, 105.17, 80.51, 78.97, 51.49, 45.87, 37.58, 37.36, 36.76, 33.79, 33.35, 25.34, 25.16, 22.89, 19.87, 12.85. HRMS (ESI+): m/z calcd for $C_{25}H_{29}N_5O_4$ $[M+H]^+$: 464.2292, found 464.2249.

Artemisinin derivative 177d: 176 (100 mg, 0.31 mmol), 4-azidobenzonitrile (60.6 mg, 0.38 mmol), CuTc (5.97 mg, 0.03 mmol). Dry DMF (0.5 mL). Reaction time was 12 h. The product was purified by flash column chromatography (EtOAc/heptane = 1:9) to afford **177d** (110 mg, 73%) as an off-white semi solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.60 (s, 1H), 7.53 – 7.49 (m, 1H), 7.41 (t, *J* = 7.8 Hz, 1H), 7.29 (s, 1H), 5.59 (s, 1H), 4.92 – 4.77 (m, 2H), 3.40 – 3.31 (m, 1H), 3.04 – 2.95 (m, 1H), 2.41 (td, *J* = 14.1, 3.8 Hz, 1H), 2.07 – 1.95 (m, 2H), 1.73 – 1.62 (m, 5H), 1.48 – 1.40 (m, 1H), 1.37 – 1.32 (m, 1H), 1.30 (d, *J* = 6.9 Hz, 6H), 1.27 (s, 3H), 1.13 (d, *J* = 7.3 Hz, 3H), 0.97 (d, *J* = 6.3 Hz, 3H), 0.90 – 0.77 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.26, 151.10, 145.57, 137.27, 129.69, 126.91, 121.55, 118.79, 118.01, 105.10, 80.50, 78.70, 51.54, 45.96, 37.51, 37.07, 36.80, 34.33, 33.82, 33.30, 25.38, 25.17, 24.00, 23.98, 22.81, 19.86, 12.90. HRMS (ESI+): m/z calcd for $C_{27}H_{36}N_4O_4$ $[M+H]^+$: 481.2809, found 481.2817.

Artemisinin derivative 177e: 176 (100 mg, 0.31 mmol), ethyl 2-azidoacetate (40.4 mg, 0.38 mmol), CuTc (5.97 mg, 0.03 mmol). Dry DMF (0.5 mL). Reaction time was 12 h. The product was purified by flash column chromatography (EtOAc/heptane = 1:9) to afford **177e** (68.8 mg, 49%) as an off-white semi solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (s, 1H), 5.48 (s, 1H), 5.21 – 5.04 (m, 2H), 4.89 – 4.70 (m, 2H), 3.78 (s, 3H), 3.33 (qd, *J* = 7.3, 4.6 Hz, 1H), 2.46 – 2.33 (m, 1H), 2.05 – 1.94 (m, 2H), 1.74 (s, 1H), 1.71 – 1.61 (m, 2H), 1.60 – 1.50 (m, 1H), 1.43 –

1.37 (m, 1H), 1.36 – 1.29 (m, 1H), 1.26 (s, 4H), 1.11 (d, *J* = 7.3 Hz, 3H), 0.96 (d, *J* = 6.2 Hz, 3H), 0.92 – 0.84 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.25, 166.73, 145.43, 124.82, 105.07, 80.41, 78.52, 53.06, 51.49, 50.78, 45.94, 37.46, 37.10, 36.76, 33.80, 33.25, 25.32, 25.12, 22.67, 19.84, 12.84. HRMS (ESI+): m/z calcd for $C_{21}H_{30}N_4O_6$ $[M+H]^+$: 435.2237, found 435.2234.

Artemisinin derivative 177f: 176 (100 mg, 0.31 mmol), (3S,4S)-2-azido-5-((benzoyloxy)methyl)tetrahydrofuran-3,4-diyl dibenzoate (183 mg, 0.38 mmol), CuTc (5.97 mg, 0.03 mmol). Dry DMF (0.5 mL). Reaction time was 12 h. The product was purified by flash column chromatography (EtOAc/heptane = 1:9) to afford **177f** (119 mg, 47%) as an off-white semi solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.32 (s, 1H), 8.06 – 8.01 (m, 2H), 7.99 – 7.91 (m, 4H), 7.77 (s, 1H), 7.62 – 7.52 (m, 3H), 7.48 – 7.34 (m, 6H), 6.38 (d, *J* = 3.2 Hz, 1H), 6.21 (dd, *J* = 5.2, 3.2 Hz, 1H), 6.13 (t, *J* = 5.6 Hz, 1H), 5.04 – 4.94 (m, 2H), 4.87 (dd, *J* = 9.5, 4.8 Hz, 1H), 4.75 (dd, *J* = 12.2, 3.6 Hz, 1H), 4.60 (dd, *J* = 12.2, 4.9 Hz, 1H), 3.43 (p, *J* = 6.9 Hz, 1H), 2.69 – 2.61 (m, 1H), 2.57 – 2.47 (m, 1H), 2.39 – 2.29 (m, 1H), 2.12 (s, 3H), 2.08 – 2.02 (m, 1H), 1.86 – 1.72 (m, 4H), 1.64 – 1.52 (m, 2H), 1.51 – 1.38 (m, 1H), 1.16 (d, *J* = 6.9 Hz, 3H), 1.06 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 212.30, 209.03, 177.55, 171.26, 166.21, 165.19, 165.11, 162.25, 143.84, 133.97, 133.79, 133.48, 129.97, 129.90, 129.39, 128.74, 128.69, 128.68, 128.61, 128.59, 122.66, 90.39, 81.17, 75.33, 71.80, 63.90, 60.50, 56.90, 55.09, 41.31, 40.52, 37.19, 35.28, 34.60, 30.53, 30.01, 21.16, 20.58, 20.19, 16.66, 14.31. HRMS (ESI+): m/z calcd for $C_{44}H_{46}N_4O_{11}$ $[M+H]^+$: 807.3235, found 807.3228.

Artemisinin derivative 177g: 176 (100 mg, 0.31 mmol), 5-azido-2-(((4-chlorobenzoyl)oxy)methyl)tetrahydrofuran-3-yl 4-chlorobenzoate (137 mg, 0.38 mmol), CuTc (5.97 mg, 0.03 mmol). Dry DMF (0.5 mL). Reaction time was 12 h. The product was purified by flash column chromatography (EtOAc/heptane = 1:9) to afford **177g** (102 mg, 43%) as a white solid m.p. 99.3 – 100.3 ˚C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.35 (s, 1H), 8.01 – 7.90 (m, 4H), 7.73 (s, 1H), 7.46 – 7.40 (m, 4H), 6.40 (t, *J* = 6.2 Hz, 1H), 5.78 (dt, *J* = 6.6, 3.4 Hz, 1H), 5.07 – 4.94 (m, 2H), 4.65 –

4.59 (m, 1H), 4.58 – 4.45 (m, 2H), 3.45 (p, *J* = 6.9 Hz, 1H), 3.33 – 3.23 (m, 1H), 2.86 – 2.77 (m, 1H), 2.70 – 2.61 (m, 1H), 2.56 – 2.46 (m, 1H), 2.38 – 2.26 (m, 1H), 2.12 (s, 3H), 2.11 – 2.02 (m, 2H), 1.87 – 1.73 (m, 3H), 1.68 – 1.53 (m, 2H), 1.51 – 1.43 (m, 1H), 1.17 (d, *J* = 6.9 Hz, 3H), 1.07 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 212.27, 208.97, 165.33, 165.05, 162.30, 143.90, 140.36, 139.95, 131.26, 131.24, 129.08, 129.02, 127.96, 127.64, 122.38, 88.64, 83.43, 75.29, 64.30, 56.84, 55.08, 41.30, 40.39, 37.80, 37.11, 34.63, 30.31, 30.02, 20.61, 20.18, 16.58. HRMS (ESI+): m/z calcd for $C_{37}H_{40}Cl_2N_4O_9$ $[M+H]^+$: 755.2244, found 755.2245.

7.4.3 Synthesis of 1,5-disubstituted and fused 1,2,3-triazoles

The compounds **177a** to **177l** and **173a** to **173d** were prepared using the method of the previous report and the spectroscopic data were consistent with the previous report[20].

7.4.4 Biological assays

Cell proliferation

Human cervical carcinoma (HeLa) cells were seeded in 96-well plates at 15,000 cells/well in the presence of 5-fold dilutions of the compounds. After 3 days of incubation, the cells were trypsinized and counted by means of a Coulter counter (Analis, Belgium). Human dermal microvascular endothelial (HMEC-1) cells were seeded on gelatin-coated 48-well plates at 20,000 cells/well. After overnight incubation, 5-fold dilutions of the compounds were added. Three days later, the cells were trypsinized and counted. Human T-cell leukemia (CEM) cells were seeded in 96-well plates at 60,000 cells/well in the presence of the compounds, allowed to proliferate for 4 days and then counted. The 50% inhibitory concentration (IC_{50}) was defined as the compound concentration required to reduce cell proliferation by 50%.[23]

7.5 Notes and references

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General Conclusion and Outlook

In this PhD research, various methodologies towards functionalized 1,2,3-triazoles as well as their biological evaluation against viral and cancer cell lines have been presented. A brief summary of previously discovered organocatalyzed methodologies towards functionalized 1,2,3-triazoles as well as their biological study and the synthesis of biological active molecules containing triazole as a core unit has been presented concisely.

Organocatalytic multicomponent reactions towards the synthesis of trisubstituted 1,2,3-triazoles have not been discovered broadly. In this thesis we have described a universal approach to access 1,2,3-triazole derivatives in a single step from simple and readily available enolizable carbonyl compounds and amines which could be considered not as the end point, but as the initial point for the rapid generation of complex triazole derivatives that are inaccessible by other means. We successfully illustrated the utility of this reaction in natural products by systematically transforming them into diverse triazole derivatives. After successful investigation of the tri-substituted 1,2,3-triazoles synthesis we have focused on synthesizing *NH*-triazole derivatives by replacing primary amines with ammonium acetate salt in previously discovered methodology. The combination of enolizable ketones, 4-nitrophenyl azide and NH_4OAc has shown to be a powerful method to achieve various mono-, di- or fused *NH*-triazole derivatives. Extension of the protocol to the direct conversion of compounds containing multiple keto groups to the corresponding triazole heterocycles in a safe manner is especially notable. Importantly, this new reaction provides an operationally simple pathway for the triazolization of natural products containing enolizable ketone functionalities.

Although there are many organo- and metal-catalytic methodologies reported towards functionalized 1,2,3-triazoles, but there have been no reports describing the synthesis of propargyl substituted triazoles in single step. In this thesis we have described a synthetic methodology

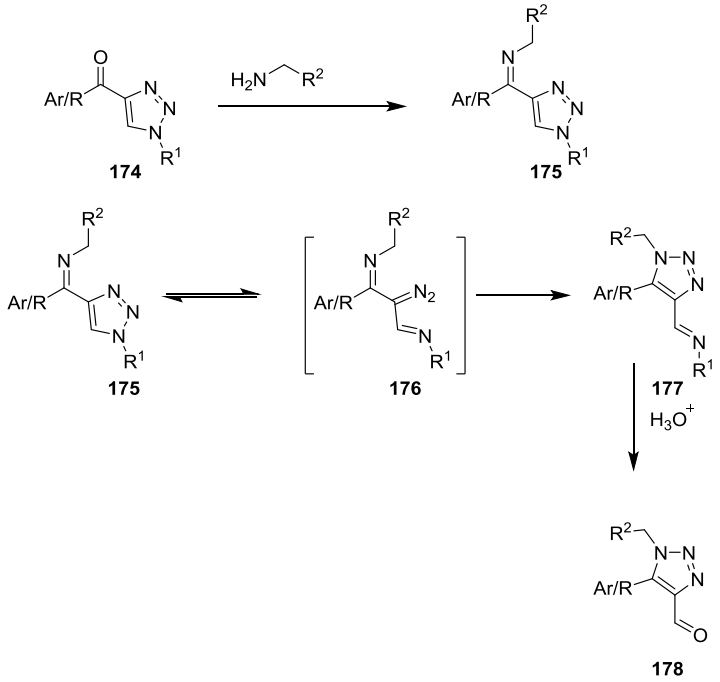
towards propargyl triazoles in a single step from readily available substrates. We have developed a highly efficient and regiospecific $Zn(OAc)_2$ mediated synthesis of propargyl functionalized triazole derivatives in a single step from ketones and propargyl amine. Subsequently, Cu(I) reactions of these propargyl triazoles with various organic azides having supramolecular and medicinal interest lead to novel N-C linked bis-triazole moieties in a regioselective manner with excellent yield. This newly developed method has following advantages: (1) it gives access in a single step to propargyl triazoles, which is not possible by any other reported methods (2) it uses cheap and readily available building blocks, (3) it can be extended to natural products containing enolizable ketone groups.

The bis triazoles formed via click reaction of propargyl triazoles can be decomposed to corresponding azavinyl carbenes which undergo various transformation leading to interesting heterocyclic moieties. In this thesis, we have disclosed an unprecedented selective decomposition of bis(1,2,3-triazoles) by a Rh(II)-catalyzed [3 + 2]-intramolecular annulation reaction which leads to the formation of 3,4-fused indoles. Extension of this protocol to heterocycles led to interesting polyfused 1,2,3-triazole derivatives. This protocol presents a simple, one-step, and atom economic efficient method for the synthesis of 1,2,3-triazole fused dihydroindoles and indoles, which could so far not be synthesized by other means.

At the last stage of this PhD thesis, a series of newly functionalized artemisinin derivatives has been prepared by using a organocatalytic multicomponent reaction. The starting precursors **169** and **171** were used for triazolisation reaction resulting in formation of fused and 1,5-disubstituted 1,2,3-triazole derivatives. All derivatives were screened against HIV I and three molecules exhibited moderate activity. The beta-tetralone derivatives **170b**, **170c**, and **170e** were inhibitory to HIV-1 replication in cell culture with a limited cytotoxicity. However, no inhibitory activity was observed against HIV-2 and an NNRTI-resitant double RT mutant (K103N; Y181C) HIV-1 strain (RES056), pointing at an NNRTI-type mode of action for the active derivatives.

Furthermore we have developed the synthetic methodology to access the propargyl substituted aza-artemisinin, further functionalization with azide via click reaction resulted in formation of various 1,4-disubstituted 1,2,3-triazoles. All the synthesized compounds were tested for their anticancer activity against 2 cancer cell lines and 1 endothelial cell line. The highest activity was found for compound **170d** with IC_{50} values of 0.92 µM and 1.2 µM in CEM and HeLa cells, respectively. Moreover, compound **170d** proved to be 30-fold more active in tumor versus endothelial cells, pointing to a potential tumor-selective mechanism of action.

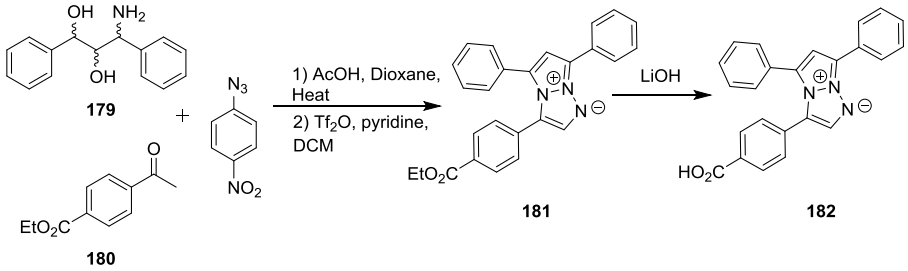
Aldehydes are well known building blocks for various heterocyclic molecules. In addition, aldehydes are used as starting materials for the preparation of various coordination polymers in the study of metal organic frameworks. By considering the utility of aldehyde functionalities, in the future, we will investigate the synthesis of various aldehyde substituted triazoles **178**. The aldehyde substituted triazoles can be prepared via Cornforth type rearrangement of acyl triazoles **174** and primary amines.



Scheme 43 synthesis of aldehyde triazoles

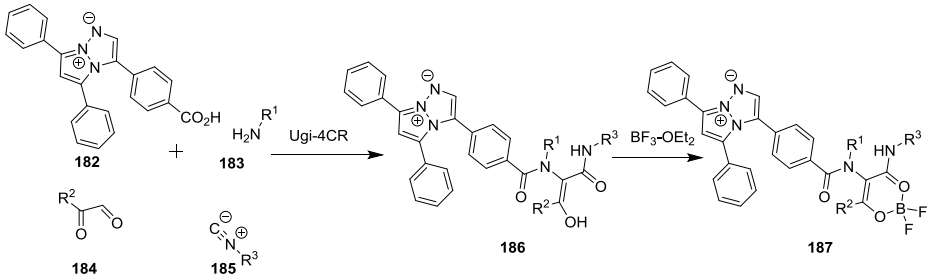
These novel aldehyde substituted triazoles can be used to synthesize various materials such as BODIPY and porphyrins. We will also investigate the application of this type of molecule in material and supramolecular chemistry.

The novel triazolization reaction can also be used to develop triazole based fluorescent molecules. We will utilize triazolization reaction with suitable substrate followed by cyclization leading to formation of triazapentalene derivatives **181**, the triazapentalene derivatives upon hydrolysis will deliver triazapentalene bearing carboxylic acid derivatives (**182**) amenable to further derivatization (Scheme 44).



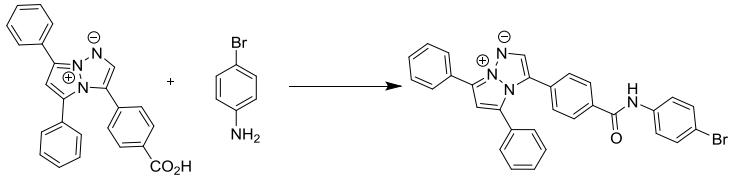
Scheme 44 synthesis of triazapentalene bearing carboxylic

The carboxylic acid bearing triazapentalene can be used in a four-componant Ugi reaction followed by complexation with boron to produce a large variety of multichromophoric hybrid molecules (**187**). (Scheme 45)

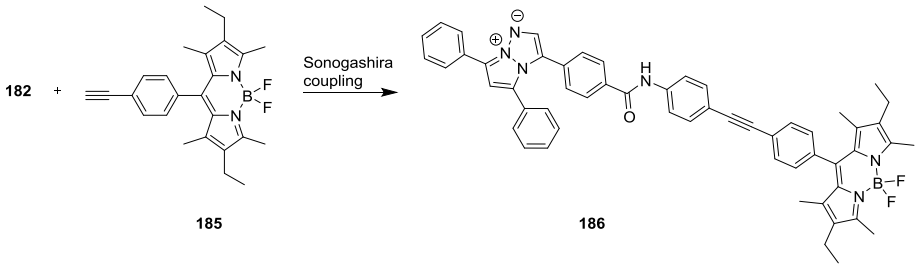


Scheme 45 Ugi reaction followed by boron complexation

Furthermore, the carboxylic acid bearing triazapentalene (**182**) is subjected to amide coupling reaction to produce triazapentalene containing bromoaryl functionality (**184**). The fluorescent molecule **184** can undergo various Pd catalyzed reactions for later stage modification with other fluorescent molecules to produce hybrid chromophoric molecules (**186**).



182 **183** **184**



185 **186**

List of Abbreviations

DCM	dichloromethane
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
EI	Electron Impact
ESI-MS	Electron spray ionization-mass spectrometry
EtOAc	Ethyl acetate
EtOH	Ethanol
^{1}H NMR	Proton nuclear magnetic resonance
HRMS	High resolution mass spectomery
TLC	Thin layer chromatography
DBU	1,8-Diazabicycloundec-7-ene
DCM	Dichloromethane
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
HeLa	Cell line derived from cervical cancer cells taken from Henrietta Lacks
HIV	Human Immunodeficiency Virus
HMEC-1	Human dermal microvascular endothelial cell line
IC_{50}	Half maximal inhibitory concentration

MCR	Multicomponent reaction
MeI	Methyl Iodide
MeOH	Methanol
PE	Petroleum Ether
4NPA	4-Nitrophenyl azide
rt	Room temperature
RuAAC	Ruthenium(II)-catalysed azide-alkyne cycloaddition
CuAAC	Copper(I)-catalysed azide-alkyne cycloaddition
SPAAC	Strain-Promoted azide-alkyne cycloaddition
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
MS	Molecular sieve
Cp*	1,2,3,4,5-Pentamethylcyclopentadiene

Safety Aspects

The laboratory work was performed in this thesis while following the safety guidelines from the departmental safety brochure. The specific information and precautions can be found at the website of the HSE service.
https://admin.kuleuven.be/sab/vgm/algemeen/EN
The general risk assessment is RA_MDS4_2014_0020_Synthesis of 1,5-disubstituted 1,2,3-triazoles
It is recommended to look the MSDS for all chemicals and catalysis before setting up the experiments. In this thesis work various ketones, amines were used as starting materials which can be found in the KU Leuven database for Hazardous compounds.

Sodium azide (NaN_3)
NaN_3 is a highly toxic compound. In order to avoid the formation of hazardous and toxic HN_3, acids should not be used in a reaction with NaN_3. Also chlorinated solvents should be avoided. At the end of the reaction solvents should be removed carefully due to possibility of explosive decomposition.

Organic azides
Organic azides such as 4-nitrophenyl azide and tosyl azide are potentially explosive in nature and should be kept in a cool place, therefore they should not be heated unless they are diluted with solvents.

Solvents
Halogenated solvents: DCM, $CHCl_3$, and DCE are very toxic and carcinogenic solvents
THF: highly flammable and irritating to respirotary system.
DMF: DMF is highly toxic by inhalation and it is also a flammable solvent.

DMSO: DMSO can cause headaches and itching and burning on contact with the skin
Methanol: Methanol is a highly flammable solvent.
Reagents
Before repeating any reaction in this thesis, it is highly recomended to check the risk assessments for a particular reagent.
Acetic Acid: Acetic acid can cause severe burning marks and corrosive as well.
Boron trifluoride diethyl etherate: It can cause severe eye damage and skin burns. It is highly flammable. Always keep in a cool place.
Rh-catalyst: It may cause digestive tract irritation.

List of publications

1. **Jana, S**.; Vroemans, R.; Dehaen, W. Synthesis of 3,4-fused triazoles by Rh catalyst: A selective decomposition of triazoles. *Adv.Synth. Catal. 2017, 359, 3085.*

2. **Jana, S.;** Thomas, J.; Dehaen, W. A One-Pot Procedure for the Synthesis of "Click-Ready" Triazoles from Ketones. *J. Org. Chem.* 2016, 81, 12426.

3. **Jana, S.**; Iram, S.; Thomas, J.; Liekens, S.; Dehaen, W. Synthesis and anticancer activity evaluation of novel (aza)artemisinin derivatives. *Bioorganic and medicinal chemistry.* 2017, 25, 3671.

4. **Jana, S.**; Iram S.; Thomas, J.; Hayat, M. Q.; Pannecouque, C.; and Dehaen, W. Application of the Triazolization Reaction to Afford Dihydroartemisinin Derivatives with Anti-HIV Activity *Molecules* **2017**, 22, 303.

5. Thomas, J.; **Jana S.**;(***Thomas J. and Jana S. shared authorship in this manuscript***) Liekens, S.; Dehaen, W. A single-step acid catalyzed reaction for rapid assembly of NH-1,2,3-triazoles. *Chem. Commun*. **2016**, 52, 9236.

6. Thomas. J.; **Jana, S**.; Sonawane M.; Fiey B.; Balzarini J.; Liekens S.; and Dehaen, W. A New Four-Component Reaction Involving Michael Addition and Gewald Reaction, Leading to Diverse Biologically Active 2-Aminothiophenes. *Organic & Biomolecular Chemistry.* 2017, 15, 3892. (*Selected as a Hot Article in Organic and Biomolecular Chemistry)*

7. Thomas, J.; **Jana, S**.; John, J.; Liekens, S.; Dehaen, W. A General Metal-Free Route Towards the Synthesis of 1,2,3-Triazoles from Readily Available Primary Amines and Ketones. *Chem. Commun*. **2016**, 52, 2885. Selected as a cover picture.